MTA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events (review of Technology Appraisal No. 90)

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TABLE OF CONTENTS:

TABLES:

FIGURES:

1 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations:

ACS	acute coronary syndromes
AE	adverse event
AG	Assessment Group
ASA	acetylsalicylic acid (ie aspirin)
BHF	British Heart Foundation
B-I	Boehringer Ingelheim
BMS/SA	Bristol-Myers Squibb/Sanofi Aventis
BNF	British National Formulary
CAD	coronary artery disease
CAPRIE	Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events
CEAC	cost-effectiveness acceptability curve
CHD	coronary heart disease
CHF	congestive heart failure
CHMP	Committee for Medicinal Products for Human Use (CHMP)
CI	confidence interval
CLOP	clopidogrel
CVD	cardiovascular disease
DM	diabetes mellitus
DP	Dipyridamole
EE	economic evaluation
EMA	European Medicines Agency
ESPS-2	Second European Stroke Prevention Study
ESPRIT	European/Australasian Stroke Prevention in Reversible Ischaemia Trial
GI	Gastrointestinal
HR	hazard ratio
HRQoL	health related quality of life
ICER	incremental cost-effectiveness ratio
IHD	ischaemic heart disease
INB	incremental net benefit
IS	ischaemic stroke
ITT	intention to treat
LY	life year
MHRA	Medicines and Healthcare products Regulatory Agency
MI	myocardial infarction
MIMS	Monthly Index of Medical Specialties
MRD	modified-release dipyridamole
MS	manufacturer's submission
MTC	mixed treatment comparison
MVD	multivascular disease
NSTEMI	non ST-segment elevation myocardial infarction
NMA	network meta-analysis
OHE	other haemorrhagic event
OR	odds ratio
OVD	other vascular death
OVE	occlusive vascular event
PAD	peripheral arterial disease
PPI	proton pump inhibitor
PRoFESS	Prevention Regimen For Effectively avoiding Second Strokes
PSA	probabilistic sensitivity analysis
QALY(s)	quality adjusted life year(s)
QoL	quality of life
RCT	randomised controlled trial
RR	relative risk
RRR	relative risk reduction
SD	standard deviation
SR	systematic review
STEMI	ST-segment elevation myocardial infarction
TIA	transient ischaemic attack
WTP	willingness to pay

Definitions of terms

Acute coronary syndromes (ACS)	Acute coronary artery disease including unstable angina and non ST-segment elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction (STEMI)
Antiplatelet agent	Type of anti-clotting agent that works by inhibiting blood platelets. Antiplatelet drugs include clopidogrel, dipyridamole and ASA
Cerebrovascular	Pertaining to the blood vessels of the brain
Clopidogrel	A thienopyridine - an inhibitor of platelet aggregation
Coronary arteries	The arteries that supply the heart muscle with blood
Coronary artery disease (CAD)	Gradual blockage of the coronary arteries, usually by atherosclerosis
Coronary heart disease (CHD)	Narrowing or blockage of the coronary arteries of the heart by atheroma; often leads to angina, coronary thrombosis or heart attack, heart failure and/or sudden death
Cost effectiveness	The consequences of the alternatives are measured in natural units, such as years of life gained. The consequences are not given a monetary value
Dipyridamole	Inhibitor of platelet aggregation, also available in combination with aspirin
Electrocardiogram (ECG)	A recording of the electrical signals from the heart
Haemorrhagic stroke	Death of brain cells due to bleeding in the brain
Heterogeneity	Between-study variation. If heterogeneity exists the pooled effect size in a meta-analysis has no meaning.
Infarction	Death of tissue following interruption of the blood supply
Intention-to-treat (ITT) analysis method	A method of data analysis in which all patients are analysed in the group they were assigned to at randomisation regardless of treatment adherence
Intermittent claudication	The most common PAD symptom, characterised by calf, thigh or buttock pain and weakness brought on by walking. Pain disappears on resting the affected limb
Ischaemia	A low oxygen state usually due to obstruction of the arterial blood supply or inadequate blood flow leading to hypoxia in the tissue
Ischaemic stroke (IS)	Death of brain cells caused by blockage in a cerebral blood vessel
Meta-analysis	A quantitative method for combining the results of many studies into one set of conclusions
Myocardial infarction (MI)	Damage to heart muscle caused by obstruction of circulation to a region of the heart. Also called a heart attack
Non ST-segment elevation MI (NSTEMI)	A myocardial infarction not associated with elevation of the ST-segment on an ECG
Occlusive vascular event (OVE)	An event caused by the blockage of an artery, such as MI, unstable angina, IS, TIA or PAD
Peripheral arterial disease (PAD)	A condition in which the arteries that carry blood to the arms or legs become narrowed or clogged, slowing or stopping the flow of blood. Also known as peripheral vascular disease (PVD)
Plaque	Atheromatous plaque is a swelling on the inner surface of an artery produced by lipid deposition
Quality-adjusted life-year(s) (QALYs)	An index of survival that is weighted or adjusted by a patient's quality of life during the survival period. QALYs are calculated by multiplying the number of life years by an appropriate utility or preference score
Qualifying event	The event (MI, IS, TIA or PAD) for which patients are randomised into a trial
Relative risk (RR)	The proportion of diseased people among those exposed to the relevant risk factor divided by the proportion of diseased people among those not exposed to the risk factor.
Relative risk reduction (RRR)	Alternative way of expressing relative risk. It is calculated as: RRR= (1 – RR) x100%. The RRR can be interpreted as the proportion of the baseline 'risk' which was eliminated by a given treatment, or by avoidance of exposure to a risk factor
ST-segment elevation MI STEMI	A myocardial infarction associated with elevation of the ST-segment on the ECG
Stroke	The sudden death of brain cells due to a lack of oxygen when blood flow to the brain is impaired by blockage or rupture of an artery to the brain causing neurological dysfunction
Thrombus	An aggregation of blood factors, primarily platelets and fibrin with entrapment of cellular elements, frequently causes vascular obstruction at the point of its formation.
Transient ischaemic attack (TIA)	A brain disorder caused by temporary disturbance of blood supply to an area of the brain, resulting in a sudden, brief (less than 24 hours, usually less than 1 hour) decrease in brain functions.
Unstable angina	Angina pectoris (chest pain) in which the cardiac pain has changed in pattern, or occurs at rest
Vascular disease	Any disease of the circulatory system

2 EXECUTIVE SUMMARY

2.1 Background

Occlusive vascular events (OVE) such as myocardial infarction (MI), ischaemic stroke (IS) and transient ischaemic attack (TIA) are the result of a reduction in blood flow associated with an artery becoming narrow or blocked through atherosclerosis and atherothrombosis. Patients with a history of such events have an increased risk of recurrence when compared to the general population. Peripheral arterial disease (PAD) is the result of narrowing of the arteries that supply blood to the muscles and other tissues, usually in the lower extremities. Patients with symptomatic PAD (typically intermittent claudication) are at increased risk of experiencing an initial OVE. Given the nature of the health problem, some people have multivascular disease (MVD), that is disease in more than one vascular bed and appear to be at even greater risk of death, MI or stroke than those with disease in a single bed. The primary objective in the treatment of all patients with a history of OVEs and PAD is to prevent the occurrence of new OVEs.

2.2 Objectives

The purpose of this review is to assess the clinical effectiveness and cost effectiveness of clopidogrel and modified-release dipyridamole (MRD) alone or with aspirin (ASA) compared with ASA (and each other, and where appropriate) in the prevention of OVEs in patients with a history of MI or IS/TIA or established PAD. The final scope issued by NICE also called for consideration of the effectiveness of clopidogrel in patients with MVD.

This review is an update and focuses on relevant clinical and cost-effectiveness evidence that has become available since publication of NICE guidance TA90: Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events.

2.3 Methods

Search strategy: Four electronic databases were searched for randomised controlled trials (RCTs) and economic evaluations (EEs).

Interventions and comparators: studies that compared clopidogrel, MRD, MRD+ASA with ASA or with each other were considered.

Patient populations: For clopidogrel, patients with a history of MI or IS or established PAD were included. For MRD, patients with a history of IS or TIA were included.

Outcomes: Data on any of the following outcomes were included in the assessment of clinical effectiveness: MI; stroke; TIA; death; AEs including bleeding complications. For the

assessment of cost effectiveness, outcomes included incremental cost per life years gained (LYG) and incremental cost per QALY gained.

Application of inclusion/exclusion criteria: Two reviewers independently screened all titles and/or abstracts including economic evaluations. The full manuscript of any publication judged to be relevant by a reviewer was obtained and assessed for inclusion or exclusion. The relevance of each publication was assessed by two reviewers; any discrepancies were resolved by consensus and where necessary, a third reviewer was consulted.

Data extraction and quality assessment: Data relating to both study design and quality were extracted by two reviewers who cross-checked each other's extraction and a third independent reviewer checked for accuracy and was consulted in cases of disagreement. Where multiple publications of the same study were identified, data were extracted and reported as a single study.

Methods of analysis/synthesis: The results of clinical and economic data extraction and quality assessment are summarised in structured tables and as a narrative description. For a variety of clinical effectiveness outcomes, indirect analysis (using a MTC methodology) was performed. Using data provided by the manufacturer of clopidogrel, within-trial time to event rates were explored as was the clinical effectiveness of clopidogrel compared with ASA for patients with MVD.

2.4 Results

Number and quality of studies: two good quality RCTs were identified, ESPRIT and PRoFESS; these were considered along with CAPRIE and ESPS-2, which were already identified in TA90. The interventions and patient populations across the four trials differed: CAPRIE compared clopidogrel with ASA in patients with a qualifying event of MI, IS or PAD; ESPS-2 compared MRD+ASA with ASA, MRD alone and placebo in patients with a qualifying event of IS/TIA; ESPRIT compared MRD+ASA with ASA in patients with a qualifying event of IS/TIA; PRoFESS compared clopidogrel with MRD+ASA in patients with a qualifying event of IS.

Eleven economic evaluations were identified from a possible 34 publications. Four studies described a UK population. The main interventions described in the studies were clopidogrel; MRD alone; MRD+ASA and ASA.

Summary of benefits and risks

RCTs: In CAPRIE, statistically significant outcomes in favour of clopidogrel were noted for the primary outcome (first occurrence of IS, MI, or vascular death) compared with ASA (overall population). However, the benefit appeared to be very small; the boundaries of the confidence intervals raise the possibility that clopidogrel is not more beneficial than ASA. In the subgroup analysis, a statistically significant difference in primary outcome was identified for patients with established PAD only.

In ESPS-2, on the first primary outcome of stroke, statistically significant differences in favour of MRD+ASA were observed in comparison with ASA and MRD alone. No other primary outcome (all cause death; stroke and all cause death) showed statistically significant differences between any two treatment arms.

In ESPRIT, on the primary outcome (first occurrence of death from all vascular causes, non-fatal stroke, non-fatal MI, or major bleeding complication) the risk of event occurrence was statistically significantly lower in the MRD+ASA arm compared to the ASA arm.

In PRoFESS, the rate of recurrent stroke of any type (primary outcome) was very similar in the MRD+ASA and clopidogrel groups and the null hypothesis (that MRD+ASA is inferior to clopidogrel) could not be rejected.

For adverse events (AEs), in CAPRIE patients in the clopidogrel arm experienced significantly higher rates of rash and diarrhoea compared to the patients in the ASA arm. In the ASA arm, patients reported significantly more incidences of indigestion/nausea/vomiting and abnormal liver function. The numbers of patients experiencing gastrointestinal (GI) haemorrhage were greater in the ASA arm compared to clopidogrel, a result reported to be statistically significant. The rates of trial discontinuation due to AEs were similar in both arms of the trial.

In ESPS-2, there was a significant difference between each arm in the occurrence of headaches; this was greater in the arms where MRD was a feature of the treatment regime. Bleeding episodes were significantly more frequent and more often moderate or severe/fatal in treatment arms that included ASA. The rates of trial discontinuation due to AEs differed significantly, with higher rates reported in the two MRD arms than in the ASA or placebo arms. Gastrointestinal events, vomiting, diarrhoea and headache were significantly different between treatment groups.

In PRoFESS, the rates of trial discontinuation were statistically significantly different between trial arms in favour of clopidogrel. Headache was reported by many more patients in

the MRD+ASA arm. Only new or worsening congestive heart failure events were statistically different between treatment arms and favoured clopidogrel.

Indirect results: On the MTC for the IS/TIA populations, clopidogrel and MRD+ASA were significantly associated with a lower risk of recurrent stroke compared to ASA; the risk of any recurrent stroke was statistically significantly increased for MRD alone compared to clopidogrel and MRD+ASA; clopidogrel was associated with less major bleeding events than ASA. Caveats apply to the MTC due to the limited outcomes that were available for selection, the small number of trials and the use of data from subgroups from one trial. It should be further noted that these analyses include a proportion of patients with MVD.

MVD subgroup: The AG reclassified patients from CAPRIE according to their disease status (CAD/MI only, IS/TIA only, PAD only or MVD). Analyses conducted by the AG confirm the results of other studies that patients with MVD are an important clinical subgroup who often have elevated single and composite risks of future events. The AG had access to MVD data from CAPRIE only and was therefore unable to conduct similar analyses for the other identified trials.

Cost-effectiveness review: In summary, the results of the literature review of cost-effectiveness evidence appear to show that, from a health service perspective, the use of clopidogrel in patients with previous PAD, IS or MI is a cost-effective option compared with ASA in the secondary prevention of OVEs. The combination of MRD+ASA seems to be cost effective compared with any other treatment in patients with previous IS/TIA in the secondary prevention of OVEs. Some of the clinical data described in the review have been superseded by more recent RCT publications. Finally, the methods used by the authors to demonstrate clinical effectiveness in some of the economic evaluations lack detail and clarity.

Submitted economic evaluations: The two economic evaluations submitted by the manufacturers appear to meet the NICE reference case criteria. Both of the models are subject to the same criticism by the AG: each model uses an unreliable basis for long-term projection. As a consequence estimated incidence rates in the models are very volatile and should not be relied on to drive the major part of the model calculations. Since the time of submission, a price for generic clopidogrel has become available and is much lower than the branded price. As the branded price is used in the economic models submitted by the manufacturers, the estimated ICERs are no longer applicable.

2.5 Summary of Assessment Group's cost-effectiveness results

Cost-effectiveness results have been generated from the AG's economic model to address two related questions:

- which treatment strategy is most cost effective in avoiding future OVEs in each of the four specified populations?

- how does the availability of generic clopidogrel at a lower price than the branded product affect the assessment of cost effectiveness of clopidogrel containing treatment strategies?

Patients with IS/TIA:

- In all scenarios, the most cost-effective strategy begins with MRD+ASA, followed by ASA and finally clopidogrel
- In patients who are intolerant of ASA, compared to no treatment, clopidogrel followed by MRD is the most cost-effective approach, independent of both TA90 guidance and the price of clopidogrel
- In patients who are intolerant of MRD, at the branded price, the preferred strategy is ASA followed by clopidogrel, but for the generic price clopidogrel followed by ASA is more cost effective
- For patients intolerant to both ASA and MRD, only clopidogrel is available for long-term prevention and is seen to be more cost effective than no preventive therapy.

Patients with MI:

- In all scenarios, the incremental cost effectiveness of allowing clopidogrel as a subsequent therapy after failure of ASA therapy compared to ASA treatment alone is less than £7,000 per QALY gained suggesting that ASA followed by clopidogrel may be the optimal strategy for this patient group
- In patients who are intolerant of ASA, clopidogrel is a cost-effective approach independent of both TA90 guidance and the price of clopidogrel (ICERs ranging between £1,981 and £12,802 per QALY gained).

Patients with established PAD:

- In all scenarios the ICER for a strategy of clopidogrel followed by ASA when compared to ASA followed by clopidogrel appears to be well within the range considered cost effective (under £10,000 per QALY gained for branded clopidogrel and under £3,000 per QALY for generic clopidogrel), suggesting this as the optimal strategy for this patient group
- In patients who are intolerant to ASA, clopidogrel is a cost-effective approach independent of both TA90 guidance and the price of clopidogrel.

Patients with MVD:

- In all scenarios, the incremental cost effectiveness of clopidogrel followed by ASA is the most cost-effective approach, independent of both TA90 guidance and the price of clopidogrel
- In patients who are intolerant to ASA, clopidogrel is a cost-effective approach to OVE prevention independent of both TA90 guidance and the price of clopidogrel.

2.5.1 Sensitivity analyses

The sensitivity analyses (SAs) undertaken using the AG's *de novo* economic model allow the most likely sources of influential uncertainty to be identified. Firstly, there is no indication that cost and utility parameters, population characteristics or non-vascular mortality give rise to significant uncertainty in economic results. Secondly, three types of parameter are implicated in at least one of the sensitivity analyses as likely to be influential on model results – the risk of events occurring, the fatality of such events, and the likelihood that patients will cease taking the prescribed preventive medications. Thirdly, model results for the 'PAD only' population appear to be particularly vulnerable to uncertainty in event risks, which should be addressed probabilistically (provided in an addendum to follow).

2.6 Discussion

The clinical evidence base supporting the previously published NICE guidance (TA90) for the prevention of OVEs in patients with a prior history of such events and patients with PAD was constructed from two trials (CAPRIE and ESPS-2) relevant to the use of clopidogrel, MRD and ASA. Since publication of this guidance, two more relevant trials have been published (ESPRIT and PRoFESS). The evidence base underpinning this update of TA90 is therefore focussed on four RCTs. In summary, the clinical evidence appears to suggest that MRD+ASA is preferred to MRD alone and ASA in patients with a prior history of IS/TIA. There is not enough clinical evidence to make an informed decision regarding the use of MRD+ASA vs clopidogrel in patients with a prior history of IS/TIA.

All of the trials relevant to the decision problem were considered to be of good quality. However, the trials were disparate in terms of their design, patient populations, interventions and definition/reporting of outcomes (clinical and safety) which means it is difficult to compare outcomes across the trials or perform evidence synthesis with any confidence using only the summary data reported in the published studies.

As previously discussed, the availability of four good quality RCTs did not allow the comprehensive comparison of clinical and safety outcomes associated with the relevant interventions across the key populations of interest. In an effort to make best use of all available clinical information, the AG undertook a MTC and investigated outcomes, where possible, for the IS/TIA population. The AG concluded that there were no major differences in the results of the MTC and the direct estimates from head-to-head trials.

The AG, using additional data provided by the manufacturer, was able to consider the clinical and cost effectiveness of clopidogrel in patients with MVD. The AG noted that there are differences in published definitions of MVD and acknowledges that depending on the definition used, the results of clinical and economic analyses may differ. The results of the AG's *de novo* economic model demonstrate that for patients with IS/TIA, MRD+ASA followed by ASA followed by clopidogrel appears to be a cost-effective approach to the prevention of future OVEs; for patients with MI, ASA followed by clopidogrel appears to be a cost-effective approach to the prevention of future OVEs; for patients with established PAD or MVD, clopidogrel followed by ASA appears to be a cost-effective approach to the prevention of future OVEs. The AG explores whether or not the price of clopidogrel or the application of TA90 guidance affects the cost effectiveness of the different interventions considered; in all cases except one, it does not.

2.6.1 Strengths and limitations

The key strengths of the report are threefold.

Firstly, the AG was able to consider the clinical and cost effectiveness of clopidogrel in people with MVD as specified in the final scope issued by NICE. Using information provided by the manufacturer, the AG re-analysed previously published data from the CAPRIE trial and estimated the clinical and cost effectiveness of clopidogrel in this clinically important subgroup of patients. The AG confirmed the findings of other published clinical papers that patients with MVD are often at high risk of future composite and single clinical events.

Secondly, the AG did not simply address the short-term costs and benefits associated with clopidogrel and MRD; the clinical and cost effectiveness of clopidogrel and MRD is considered over time using treatment scenarios. The strength of this approach is that it reflects the real world in which many patients will need to switch between different treatments during

their lifetime. Restricting the analysis of costs and benefits of long-term prophylaxis to a few years frequently results in erroneous conclusions.

Finally, the structure of the economic model required to address the questions posed in the final scope issued by NICE necessitated careful planning and execution by the AG as well as access to further analyses of clinical data from the manufacturers. Working collaboratively, the AG was able to make best use of limited evidence and estimate relevant ICERs for individual patient populations using an economic model designed to minimise the scope for multiple cumulative bias inherent in long-term projection of multiple competing risks.

The clinical and cost-effectiveness findings of the report are limited by the nature of the clinical evidence available. For the MI, PAD and MVD patient populations, data were only available from the CAPRIE trial (clopidogrel vs ASA) and the clinical results favoured clopidogrel. However, use of a single trial to generate clinical evidence for three individual patient populations inevitably attracts criticism. It is also important to note that the CAPRIE trial did not distinguish between patients with NSTEMI and STEMI myocardial infarction and this clearly inhibits the interpretation of the trial results for these clinically important subgroups of patients. For the IS/TIA population, relevant evidence was available from four published RCTs to inform the AG's assessment of clopidogrel and MRD. However, the studies were all very different in terms of design, patient populations and clinical outcomes, so that even indirect comparisons proved to be fraught with difficulty. The key comparison of interest for patients with IS/TIA was clopidogrel vs MRD+ASA and the results of this trial were inconclusive. This is unfortunate as it is unlikely that a trial of this design will ever be repeated. In summary, the clinical evidence available, particularly for MI, PAD and MVD populations, to answer the key questions set out in the final scope is limited.

2.6.2 Uncertainties

The findings of this report for the MI, PAD and MVD patient populations are reliant on several post-hoc subgroup analyses from a single trial; this means that there is inevitable uncertainty associated with the findings of this report. The AC which developed the guidance for TA90 considered it inappropriate to rely on post-hoc analyses. However, the AG is of the opinion that reliance on the results of post-hoc subgroup analyses from a single trial was unavoidable if the questions set out in the final scope issued by NICE were to be adequately addressed in this report. To illustrate: there are clinical data available from PRoFESS, ESPS-2 and ESPRIT for the IS/TIA population, but the only clinical data available for patients with prior MI, PAD and MVD is from the CAPRIE trial. Patients with MI, PAD and MVD are not considered to constitute a single homogeneous clinical population; this means that use of subgroup analysis to estimate the clinical and cost effectiveness of clopidogrel for these individual subpopulations although not ideal is necessary. It is important to note that the size

of each of the subgroup populations is considerable (MI= 5,741; PAD= 3,713; MVD= 4,991), and proved sufficient to demonstrate important differences in risk profiles between these groups.

In the absence of any universally agreed definition, the MVD subgroup analyses were based on a population defined by the AG. The AG's definition appears to be consistent with the simplest and broadest definition described in the published literature; however, it is likely that any differences in definitions of MVD subgroups will lead to differences in patient numbers and relative risks.

Additionally, the head to head trials and the MTC results will have included subgroups of patients who had disease in more than one vascular bed as none of the trials distinguished between patients with single and multivascular disease.

2.7 Conclusions

For patients with IS/TIA, MRD+ASA followed by ASA followed by clopidogrel appears to be a cost-effective approach to the prevention of future OVEs.

For patients with MI, ASA followed by clopidogrel appears to be a cost-effective approach to the prevention of future OVEs.

For patients with established PAD or MVD, clopidogrel followed by ASA appears to be a cost-effective approach to the prevention of future OVEs.

2.8 Suggested research

It is suggested that any future trials in this area should distinguish between patients with single and multivascular disease, that definitions of MVD should be pre-specified (ideally using a common standard) and that trialists should ensure that trials are sufficiently powered over an extended follow-up period to allow detection of treatment differences between subgroups of patients. To facilitate comparison of primary and secondary outcomes across relevant trials, all outcomes need to be reported consistently and at key time points.

It would be most valuable to have well-audited data on a defined patient group from a long-term clinical registry of all UK patients treated with antiplatelet agents. Such a data source could provide a basis for research and audit to inform future assessments of antiplatelet agents in patients with single and multivascular disease over the long-term.

3 BACKGROUND

3.1 Description of the health problem

Cardiovascular disease (CVD) is an umbrella term that includes coronary heart disease (CHD), peripheral arterial disease (PAD) and cerebrovascular disease. Cardiovascular disease is commonly caused by arteries becoming narrowed through atherosclerosis; it is the main cause of death in the UK, accounting for 35% of deaths each year (almost 198,000).[1] Almost half (48%) of all CVD deaths are from CHD, with stroke making up a further quarter (28%).[1] In addition to being the main cause of death, CVD is also the major cause of premature death (under 75 years) in the UK; CVD caused 30% of premature death in men and 22% in women in 2006.[1]

Occlusive vascular events (OVE) such as myocardial infarction (MI), ischaemic stroke (IS) and transient ischaemic attack (TIA) are classified as subsets of CVD. These events are the result of a reduction in blood flow associated with an artery becoming narrow or blocked through atherosclerosis and atherothrombosis. Patients with a history of such events have an increased risk of recurrence when compared to the general population. Peripheral arterial disease (PAD) is also a subset of CVD and is the result of narrowing of the arteries that supply blood to the muscles and other tissues, usually in the lower extremities. Patients with symptomatic PAD (typically intermittent claudication) are at increased risk of experiencing an initial OVE. Given the nature of the health problem, some people have what is classified as multivascular disease (MVD), that is disease in more than one vascular bed and appear to be at even greater risk of death, MI or stroke than those with disease in a single bed.[2] Therefore, the primary objective in the treatment of all patients with a history of CVD is to prevent the occurrence of new OVEs.

3.1.1 Aetiology, pathology and prognosis

As noted earlier, the cause of OVEs is a reduction in blood flow associated with an artery becoming narrow or blocked through atherosclerosis and atherothrombosis. Atherothrombosis involves the formation of a platelet-rich thrombus, frequently at the site of a disrupted atherosclerotic plaque that leads to local occlusion or distal embolism. Atherosclerotic plaque formation occurs as a result of damage to vascular endothelium. Possible causes of damage include the following: elevated and modified low density lipoproteins (LDL); free radicals caused by cigarette smoking, hypertension and diabetes mellitus (DM); genetic alterations and combinations of these and other factors.[3]

3.1.2 Epidemiology

The five manifestations of CVD considered in this report are MI, IS, TIA, PAD and MVD.

Myocardial infarction (also known as a heart attack) is the interruption of the blood supply to the heart muscle. This is most commonly caused by occlusion of a coronary artery following the rupture of atherosclerotic plaque. The resulting restriction in blood supply and oxygen starvation can cause damage to, or the death of, the heart muscle. Typical symptoms of MI include sudden chest pain with sweating or nausea; MIs can also be symptomless. Women may experience different symptoms to men. Based on the results of changes in ECG readings, MIs are classified into two subtypes; non ST-segment elevated myocardial infarction (NSTEMI) or ST-segment elevated myocardial infarction (STEMI). The distinction has implications for future antiplatelet treatment. After a MI, a patient remains at high risk of a further MI or other OVE.

Data from 2006 for the UK demonstrate that across all ages, there were 146,000 cases of MI; 87,000 in men and 59,000 in women.[1] The incidence of MI varies across regions, between men and women and increases with age.[1] Higher incidence rates are apparent in northern areas of the UK compared to southern areas. In the UK, amongst men and women aged over 35 years, the prevalence is thought to be over 1.4 million.[1] Approximately 30% of people who experience an acute MI die before they reach hospital.[4] Patients who experience a MI and survive are likely to have a further cardiac event.[5]

There are a number of different types of stroke; however, the majority of cases (approximately 70%) are ischaemic caused through the blockage of an artery in the brain.[6] This leads to damage to or death of the brain cells due to lack of oxygen. The symptoms of stroke can include: numbness, weakness or lack of movement on one side of the body, slurred speech, difficulty finding words or understanding speech, problems with vision, confusion, and/or severe headache.[7] A stroke happens suddenly and the effects are experienced straight away.[7] Anyone who suddenly has symptoms that might be caused by a stroke should be assessed as soon as possible using a test such as FAST (Face, Arm, Speech Test) and, on arrival at hospital the ROSIER (Recognition of Stroke in the Emergency Room) may be used.[7] A stroke may be classified as disabling or non-disabling.

The British Heart Foundation (BHF) reports that approximately 98,000 people experience a first IS every year in the UK with little difference in rates between men and women and an increased risk with age.[8] Additionally they estimate from 2006 data that, in the UK, as many as 1.1 million people have experienced a stroke; this is equivalent to a prevalence rate of 1.6% in the population in England and 2% in Wales.[8] The risk of recurrent stroke is greatest in the first six months following the initial event, but a patient may remain at greater risk of stroke

than the general population for a number of years.[3] As many as 30% of strokes are thought to be recurrent.[9] Patients who have experienced a stroke are also at risk of further OVEs, including MI.[10, 11]

A TIA is a disorder caused by temporary disturbance of blood supply to an area of the brain that results in a sudden but brief decrease (less than 24 hours, usually less than one hour) in brain functions and causes stroke like symptoms. If the neurological deficit lasts more than 24 hours, it is described as a stroke. Estimates for the UK indicate that between 46,000 and 65,000 people suffer a TIA each year and prevalence of TIA is projected to be 510,000.[8] In contrast to the trend noted in stroke data, there appear to be higher rates of TIA in women; as noted for stroke, incidence and prevalence rates increase rapidly with age.[8] Patients experiencing a TIA are at high risk of suffering a subsequent stroke, with 90-day risks of stroke reported to be as high as 10.5%.[12] In patients enrolled in clinical trials after a TIA or non-disabling IS, the annual risk of important vascular events (death from all vascular causes, non-fatal stroke, or non-fatal MI) is reported as being between 4% and 11%; the corresponding estimate for population-based studies is 9% per year.[13]

Peripheral arterial disease is a condition in which the arteries that carry blood to the arms or legs become narrowed or congested, slowing or stopping the flow of blood. Approximately 20% of people aged from 55 to 75 years of age have evidence of lower extremity PAD. Since the size of the UK population aged 55 years and over is approximately 17 million, this equates to a prevalence of around 850,000.[14] It is thought that worldwide and in the UK, PAD is under-diagnosed and under-treated.[15, 16] Five percent of the people with PAD experience symptoms. The most common symptom is intermittent claudication (pain on walking) which is relieved by a short rest; however, some patients with PAD may experience significant pain and poor quality of life (QoL).[17] Over five years, about 20% of people with intermittent claudication have a non-fatal cardiovascular event (MI or stroke).[18] People with PAD, including those who are asymptomatic, have a high risk of death from MI and IS, their relative risks being two to three times that of age and sex-matched groups.[17] Coronary heart disease is the major cause of death in people with PAD of the legs.[19]

Although the diagnosis of PAD can generally be made from clinical history and examination, objective evidence of significant PAD can be made by obtaining an ankle brachial pressure index. This index is the ratio of the ankle to brachial systolic pressure and may be measured using a sphygmomanometer and handheld Doppler device.[17] Obtaining an ankle brachial pressure index is non-invasive and relatively easy, but is rarely used in clinical practice.[20]

As noted earlier, there are a number of patients with CVD who have disease in more than one vascular bed (otherwise known as MVD patients). The REACH registry (supported by

Sanofi-aventis, Bristol-Myers Squibb and Waksman Foundation) collected data from approximately 67,888 patients who were recruited from 5,473 physician practices in 44 countries worldwide.[15, 21] Patients in the registry are described as being over 45 years old with least three atherothrombotic risk factors (eg treated DM, diabetic nephropathy, ankle brachial index of less than 0.9, asymptomatic carotid stenosis of 70% or greater) or documented cerebrovascular disease, coronary artery disease (CAD) or PAD. A survey[21] of data from the REACH registry identified that 15.9% of patients had symptomatic polyvascular disease defined as coexistent symptomatic (clinically recognized) arterial disease in two or three territories (coronary, cerebral, and/or peripheral) within each patient. A further analysis indicated that rates of cardiovascular death, MI or stroke at one year increases substantially with the number of affected vascular beds.[2] This recognition of the importance of MVD, problems with its definition, and its inherent increased risk of further events is explored in section 5.7.

Trends in CHD and stroke

Coronary heart disease causes over 90,000 deaths a year in the UK: approximately one in five deaths in men and one in six deaths in women. There is geographical variation in prevalence with greater rates in the northern areas of England compared to southern areas and intermediate rates in Wales. There are also social inequalities in mortality from CHD; higher mortality is noted in people from more deprived areas and those working in manual jobs.[1]

Death rates from CHD have been declining since the late 1970s and death rates from stroke have declined in the last ten years, although these trends appear to be plateauing, particularly in younger people. It is thought that the decline in rates of CHD is due to reductions in risk factors (mainly smoking) and better treatment (including secondary prevention). Although mortality appears to be falling, CHD related morbidity is rising.[1]

Stroke accounts for around 53,000 deaths each year in the UK (approximately 9% of all deaths). According to the BHF[8] it is not possible to know how many deaths each year are attributable to each stroke subtype. However, they report that age-standardised mortality rates from stroke have decreased markedly in the last four decades, with a 90% reduction in IS mortality.[8] There is geographical variation in death rates from stroke in the UK; the highest rates are in Scotland, followed by Northern England, Wales and Northern Ireland. The South of England (particularly London) exhibits the lowest stroke mortality rates. Socio-economic inequalities in stroke mortality are evident; historically, rates have decreased more quickly in adults from higher social classes and mortality increases with deprivation.[8]

The majority of people survive an initial stroke, but often have significant morbidity.[7] Stroke causes a greater range of disabilities than any other condition and has a greater disability

impact than other chronic diseases.[22] It is thought that more than 900,000 people in England are living with the effects of stroke, with half of these being dependent on other people for help with everyday activities.[7]

Impact of health problem

In 2006/7 there were 428,000 inpatient episodes for CHD in England and over 175,000 for stroke.[1, 8] Data from 2006 underline the high cost of CHD and stroke to the UK health care system; each cost around £3.2 billion. A cost per capita of just over £50 for each condition was observed.[1] Hospital care costs for CHD accounted for 73% of the total cost whilst for stroke hospital costs accounted for 94%.[1]

Production losses from death and illness and from informal care of people with CHD and CVD are a substantial financial burden.[1] Data from 2006 for the UK demonstrate that production losses due to mortality and morbidity associated with CHD cost over £3.9 billion; 65% due to death and 35% due to illness in those of working age. Informal care costs were approximately £1.8 billion.[1] For stroke, 65% of production losses were due to illness and costs of informal care were £2.9 million, reflecting the debilitating impact of stroke on individuals.[1]

3.2 Current service provision

Management of disease

Secondary prevention of OVEs is antiplatelet therapy. Current NICE recommendations in TA90[23] for the secondary prevention of OVEs in patients with a history of IS or TIA, state that modified-release dipyridamole (MRD) in combination with acetylsalicylic acid (ASA) should be used for a period of two years from the most recent event. Thereafter, or if MRD is not tolerated, standard care (including long term, low-dose ASA) should be used. People with a history of OVEs (except TIA) or PAD who are intolerant to low-dose ASA are advised to use clopidogrel alone.

Due to the evolving nature of treatments, and the different patient groups included in this review, a number of clinical recommendations are relevant. These are described in Table 3-1.

In addition to TA90,[23] there are separate (and different) clinical recommendations for the two subtypes of MI: NSTEMI and STEMI. Clopidogrel+ASA is the recommended treatment for both types, but for a period of 12 months following an NSTEMI[24] and four weeks in the event of a STEMI. There is currently no guidance for the prevention of OVEs in patients with MVD.

Table 3-1 Patient populations and clinical recommendations

Patient population	Guidance	Clinical recommendation	Trial evidence	Trial population	Licensed indication for drug
MI	TA90 2005[23] (MTA) Clopidogrel and modified-release dipyridamole in the prevention of occlusive vascular events	CLOP if ASA intolerant	CAPRIE[25] CLOP vs ASA	33% MI 34% PAD 33% IS *No differentiation between patients with NSTEMI and STEMI*	ASA: For the secondary prevention of thrombotic cerebrovascular or cardiovascular disease; CLOP: prevention of atherosclerotic events in people with a history of MI (from a few days until less than 35 days), IS (from 7 days until less than 6 months) or established PAD CLOP+ASA: for acute coronary syndromes
MI (NSTEMI)	CG94 2010[24] (SR) Clopidogrel in the treatment of non ST-segment elevation acute coronary syndrome	CLOP+ASA for 12 months after the most recent event. Then standard care (including ASA) or clopidogrel if ASA intolerant	CURE[26] CLOP+ASA vs ASA	100%	
MI (STEMI)	CG48 2007[27] (SR) Secondary prevention in primary and secondary care for patients following a myocardial infarction	CLOP+ASA for 4 weeks after the most recent event. Then standard care (including ASA) or clopidogrel if ASA intolerant	COMMIT[28] CLOP +ASA vs ASA	93% STEMI 7% NSTEMI	CLOP+ASA: for acute coronary syndromes
IS	TA90 2005[23] (MTA) Clopidogrel and modified-release dipyridamole in the prevention of occlusive vascular events	MRD+ASA for 2 years after the most recent event. Thereafter, or if MRD is not tolerated, standard care (including long-term treatment with low-dose ASA)	ESPS-2[29] ASA vs MRD vs MRD+ASA vs placebo	76% IS 24% TIA	MRD (+/- ASA) secondary prevention of IS and TIA
TIA	TA90 2005[23] (MTA) Clopidogrel and modified-release dipyridamole in the prevention of occlusive vascular events	MRD+ASA for 2 years after the most recent event. Thereafter, or if MRD is not tolerated, standard care (including long-term treatment with low-dose ASA)			
PAD	TA90 2005[23] (MTA) Clopidogrel and modified-release dipyridamole in the prevention of occlusive vascular events	CLOP if ASA intolerant*	CAPRIE[25] CLOP vs ASA	33% MI 34% PAD 33% IS	ASA: For the secondary prevention of thrombotic cerebrovascular or cardiovascular disease; CLOP: prevention of atherosclerotic events in people with a history of MI (from a few days until less than 35 days), IS (from 7 days until less than 6 months) or established PAD
MVD	Not currently included	NA	NA	NA	NA

ASA=aspirin; MTA=multiple technology assessment; SR=systematic review; NA=not available; IS=ischaemic stroke; TIA=transitory ischaemic attack; MI=myocardial infarction; PAD=peripheral arterial disease; NSTEMI=non ST-segment elevated myocardial infarction; STEMI=ST-segment elevated myocardial infarction; MRD=modified-release dipyridamole; MVD=multivascular disease; CLOP=clopidogrel *ASA not licensed for PAD

The purpose of the current review is to update the evidence base that was available to inform NICE's TA90 guidance.[3, 23] Patient groups who are beyond its remit include: those who have had, or are at risk of, a stroke associated with atrial fibrillation, or who require treatment to prevent OVEs after coronary revascularisation or carotid artery procedures.

Although explicit data on provision of antiplatelet treatment for patients in the various disease categories is not available, general practitioner (GP) prescribing data for England from 2004-2009[30] indicate a slow and steady increase in prescribing rates over that time period (Figure 3-1).

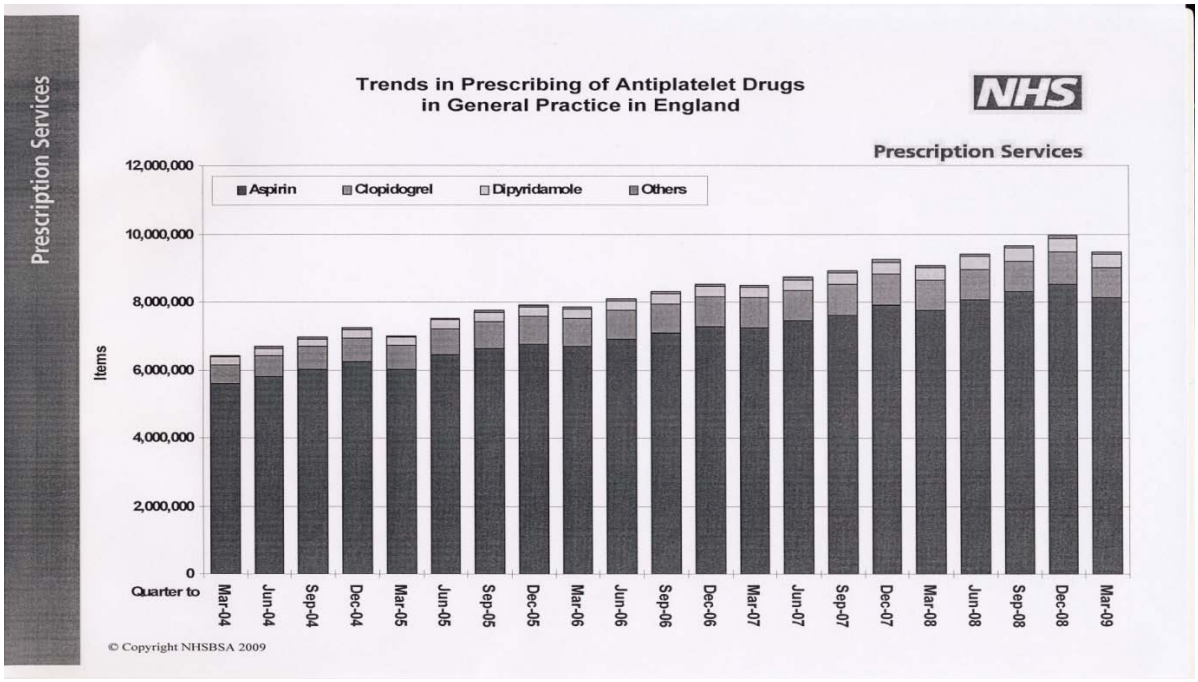

Figure 3-1 Trends in prescribing of antiplatelet drugs in general practice in England

Current service cost

The current prices for ASA, MRD and clopidogrel are shown in Table 3-2. All prices are net and are taken from the British National Formulary (BNF) 58.[31] Generic versions of clopidogrel are now licensed; from April 1st 2010 clopidogrel is listed as category M of Part VIII of the Drug Tariff meaning that pharmacists will be reimbursed at the generic price of £10.90 for 30 tablets of 75mg clopidogrel.[32, 33]

Table 3-2 Price of ASA, MRD and clopidogrel

Drug	Price per pack	Price per day
ASA (75mg) enteric coated tablets	94p per 28 £1.07 per 56	0.033 0.019
MRD+ASA dipyridamole (200mg), ASA (25mg)	£7.79 per 60	0.26 (= 2 daily doses)
MRD dipyridamole (200mg)	£7.50 per 60	0.25 (= 2 daily doses)
CLOP(Plavix) (75mg)	£36.35 per 30	£1.21

MRD= modified-release dipyridamole; ASA= aspirin; CLOP= clopidogrel

In Figure 3-2 trends in spending on the various agents prescribed by GPs in England over the period of 2004-2009 are shown.[30]

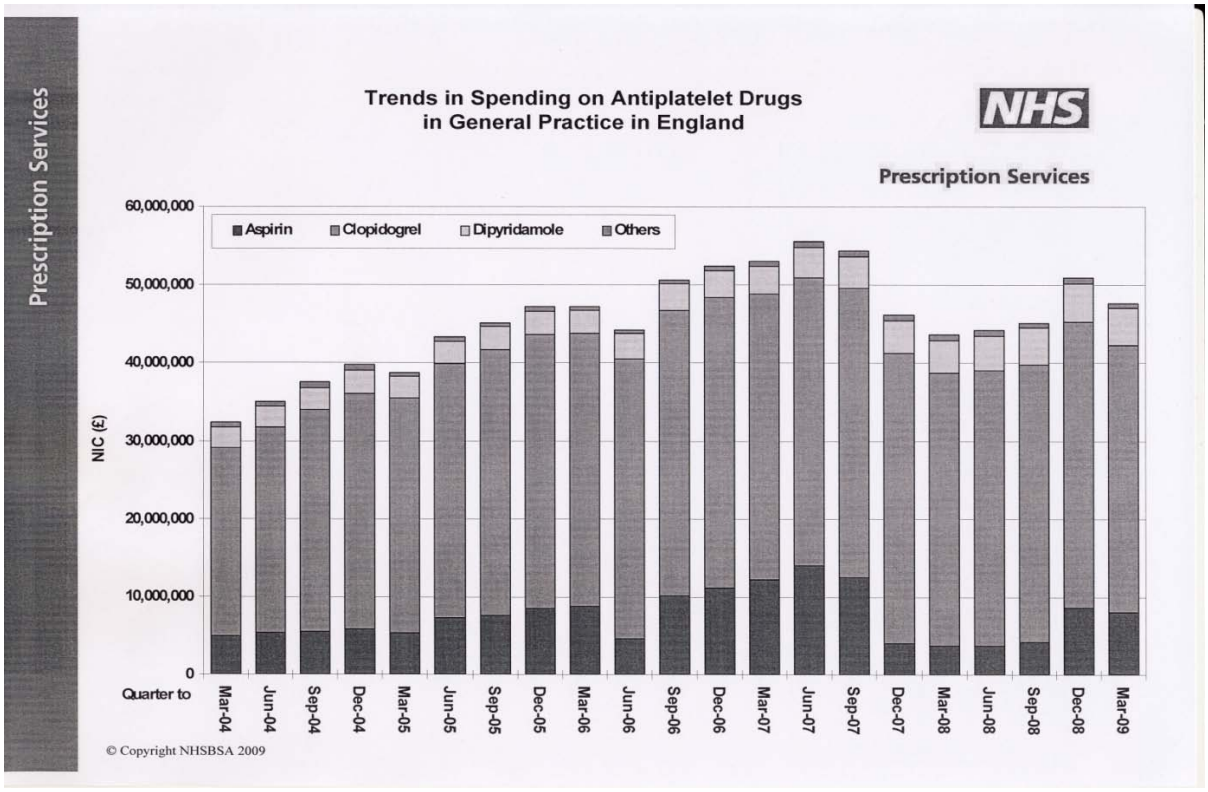

Figure 3-2 Trends in spending on antiplatelet drugs in general practice in England

Variation in services and/or uncertainty about cost

The recent end of patent term for clopidogrel has meant that a number of generic formulations of the drug have been approved by the European Medicines Agency (EMA)[34] and the Medicines and Healthcare Products Regulatory Agency (MHRA).[35] At the time of writing, there are at least eight generic products available in the UK as listed in Table 3-3. All those listed are licensed for the prevention of atherothrombotic events in patients suffering from MI (from a few days until less than 35 days), IS (from 7 days until less than 6 months) or established PAD. It is currently unclear (due to issues relating to patent) whether any of these products may also be used in combination with ASA for the treatment of ACS patients.

Table 3-3 Generic versions of clopidogrel available in the UK

Name of manufacturer	Licensed name	Active ingredient
Mylan Pharmaceuticals/Generics UK	Clopidogrel Mylan	Clopidogrel hydrochloride
Consilient Health Limited	Clopidogrel Consilient	Clopidogrel hydrochloride
Sandoz Ltd	Clopidogrel Sandoz	Clopidogrel besilate
Actavis Group PTC EHF	Actavis clopidogrel	Clopidogrel besilate
Arrow Generics	Arrow clopidogrel	Clopidogrel besilate
Dr Reddy's Laboratories (UK) Limited	Dr Reddy's clopidogrel	Clopidogrel besilate
Dexcel Pharma Limited	Dexcel clopidogrel	Clopidogrel besilate
Beacon Pharmaceuticals	Beacon clopidogrel (Grepid®)	Clopidogrel besilate

Relevant national guidelines including National Service Frameworks

The design of guidelines and frameworks is based on overall national goals and targets. The government target for England (set in 1999 and 2004) for CVD was to reduce the death rate from CHD, stroke and related diseases in people aged 75 years and under by at least two-fifths by 2010, saving up to 200,000 lives in total, with a milestone of a reduction of one-quarter by 2005.[36, 37]A further target was to reduce the inequalities gap in death rates from these diseases between the fifth of areas with the worst health and deprivation indicators and the population as a whole in people aged 75 years and under by 40% by 2010.

The Welsh Assembly Government (2005) set its target for CHD as a reduction in mortality rates in 65-74 year olds from 600 per 100,000 in 2002 to 400 per 100,00 in 2012. Its health inequality target is to improve CHD mortality in all groups and at the same time aim for a more rapid improvement in the most deprived groups. The target for stroke is to reduce mortality in people aged 65-74 years by 20% by 2012.[38, 39]

New GP contracts include points for the number of CHD and stroke patients who are taking antiplatelet therapy for secondary prevention of OVEs.[40] The contract does not appear to include patients with PAD.[41]

Use of antiplatelet agents are therefore the focus of a number of national documents including the National Service Framework[23, 42-44] and NICE guidance documents. The nature of MVD means that at times these documents apply to overlapping patient populations.

The National Service Framework (NSF) for Coronary Heart Disease: Standards and Quality Requirements (England)[1] states that GPs and primary care teams should identify all patients with established CVD and offer them comprehensive advice and appropriate treatment to reduce their risks of CHD.[42, 43]

The National Stroke Strategy: ten point plan for action for England, states that in preventing stroke, support for healthier lifestyles should be offered and action to tackle vascular risk taken.[45]

As part of the Diabetes, Heart Disease and Stroke (DHDS) prevention project, the UK National Screening Committee, commissioned The Handbook of Vascular Risk Assessment, Risk Reduction and Risk Management.[46] The handbook is designed to support local health services in meeting the standards for the prevention and early detection of CHD, set out in the NSF for England. The target population for screening is people aged between 40 and 75 years. The handbook describes the context and outlines evidence for a co-ordinated vascular disease control programme to identify and reduce risks of CVD in the general population; to suggest aims, objectives and a delivery strategy framework appropriate for a CVD risk management programme; to report key messages from the Diabetes, Heart Disease & Stroke pilot project; to provide examples of tools, resources and standard operating procedures that can be used by health professionals.[46]

3.3 Description of technology under assessment

Two antiplatelet agents, used within their respective licensed indications, are the focus of this review: clopidogrel (Plavix®, Bristol-Myers Squibb, Sanofi-aventis); MRD+ASA in a single capsule (Asasantin Retard®, Boehringer-Ingelheim) or MRD alone (Persantin Retard®, Boehringer-Ingelheim). Clopidogrel produces an immediate and sustained inhibition of ADP–induced platelet aggregation that helps prevent blood clots.[47] Dipyridamole is thought to inhibit adenosine (a potent inhibitor of platelet activation and aggregation) uptake into blood cells and vascular cells.[3] Summaries of product characteristics for clopidogrel, MRD+ASA and MRD alone are available from the Electronic Medicines Compendium (EMC).[48]

3.3.1 Clopidogrel

Clopidogrel is licensed in adults for the prevention of atherothrombotic events in patients suffering from MI (from a few days to 35 days), IS (from seven days to six months) or established PAD. Clopidogrel is available as 75mg and 300mg film coated tablets. The recommended dose is 75mg as a single daily dose taken with or without food. As previously noted generic versions of clopidogrel are now available (Table 3-3) although it is currently unclear whether any of these generic versions are licensed for prescribing with ASA for the treatment of ACS..

Contraindications for clopidogrel include: hypersensitivity to the active substance or to any of the excipients, severe liver impairment, active pathological bleeding such as peptic ulcer or intracranial haemorrhage. Special warnings for clopidogrel use include (but are not limited to) the following:

- Use with caution in combination with any other anticoagulant or antiplatelet drug or in patients with bleeding diathesis
- Thrombotic thrombocytopenic purpura (TTP) has been reported very rarely following the use of clopidogrel, sometimes after a short exposure

Based on literature data, patients with genetically reduced CYP2C19 function have lower systemic exposure to the active metabolite of clopidogrel and diminished antiplatelet responses, and generally exhibit higher cardiovascular event rates following MI than do patients with normal CYP2C19 function. Since clopidogrel is metabolised to its active metabolite partly by CYP2C19, use of drugs that inhibit the activity of this enzyme would be expected to result in reduced drug levels of the active metabolite of clopidogrel and a reduction in clinical efficacy. Concomitant use of drugs that inhibit CYP2C19 should be discouraged. Although the evidence of CYP2C19 inhibition varies within the class of proton pump inhibitors (PPI), clinical studies suggest an interaction between clopidogrel and possibly all members of this class. Therefore, concomitant use of PPIs should be avoided unless absolutely necessary. The AG is aware that new evidence has lead to a new recommendation from the EMA[49] that only two specific PPIs (omeprazole and esomeprazole) are a problem (see below).

3.3.2 Important subgroups of patients

Clopidogrel is not licensed for secondary prevention of OVEs in patients who have experienced a TIA, although in UK clinical practice, it may be prescribed for these patients if they are unable to tolerate MRD or ASA (Dr Anil Sharma, personal communication, Aintree Hospitals NHS Trust, 17/3/10).

There is evidence that two PPIs (omeprazole and esomeprazole) reduce the effectiveness of clopidogrel in preventing the recurrence of adverse cardiac events; current advice is that concomitant use of these with clopidogrel should be discouraged. In addition, the concomitant use of other known CYP2C19-inhibiting medicines with clopidogrel is discouraged because these are expected to have a similar effect to omeprazole and esomeprazole.[49]

3.4 Modified-release dipyridamole

A non-modified release (often referred to as immediate release) version of dipyridamole is available; however only the evidence for MRD is considered in this review. Modified-release dipyridamole is often also referred to as extended-release dipyridamole (ERDP). For clarity, this review will use the term MRD throughout.

Modified-release dipyridamole (alone or with ASA) is licensed for use in adults for the secondary prevention of IS and TIA. It is available in two preparations:

- Asasantin Retard (Boehringer-Ingelheim) capsules containing both dipyridamole (200mg) and ASA (25mg)
- Persantin Retard (Boehringer-Ingelheim) capsules containing dipyridamole (200mg)

The recommended dose of MRD is 200mg twice daily. Capsules should be taken in the morning and again in the evening, preferably with meals.

Contraindications for Asasantin Retard include: hypersensitivity to any component of the product or salicylates, patients with active gastric or duodenal ulcers, patients in the last trimester of pregnancy. Special warnings and precautions for use include (but are not limited to):

- Asasantin should be used with caution in patients at increased risk of bleeding and should be followed carefully for any signs of bleeding
- Caution should be advised in patients receiving concomitant medication which may increase the risk of bleeding
- Headache that may occur at the beginning of treatment should not be treated with analgaesic doses of ASA
- Among other properties, dipyridamole acts as a vasodilator. It should be used with caution in patients with severe CAD, including unstable angina or recent MI, left ventricular flow obstruction, or haemodynamic instability
- Due to the ASA component, all appropriate cautions applicable to ASA should also be observed.

Contraindications for Persantin Retard are limited to hypersensitivity to any component of the product. The same cautions should be observed as for Asasantin Retard (with the exception of those related to the ASA content).

4 DEFINTION OF THE DECISION PROBLEM

4.1 Decision problem

The remit of this appraisal is to review and update (if necessary) the clinical and cost-effectiveness evidence base described in TA90.[23] Table 4-1 shows the key elements of the decision problem of the appraisal.

Table 4-1 Key elements of the decision problem

Interventions	Clopidogrel
	MRD used alone or in combination with ASA
Patient population	For clopidogrel, adults with established PAD or those with a history of MI or IS
	For MRD, adults with a history of IS or TIA
Comparators	The interventions will be compared with ASA and, where appropriate, with each other
Outcomes	Any of the following: MI (STEMI and NSTEMI) Unstable angina Stroke Vascular death Death Adverse effects of treatment including bleeding complications Health-related quality of life Incremental cost per life year gained Incremental cost per quality adjusted life year gained
Other considerations	If the evidence allows, the effectiveness of clopidogrel in people with multivascular disease who are considered to be at high risk of recurrent OVEs, will be considered. If the evidence allows, the duration of treatment with the specified interventions will be considered

ASA=aspirin; IS=ischaemic stroke; MI=myocardial infarction; MRD=modified-release dipyridamole; NSTEMI=non ST-segment elevation myocardial infarction; OVE=occlusive vascular events; PAD=peripheral arterial disease; STEMI=ST-segment elevation myocardial infarction; TIA=transient ischaemic attack

The key elements of this appraisal are similar to those which underpin the previous review[3] with the following exceptions: patients with a history of TIA will not be considered in the assessment of the effectiveness of clopidogrel as clopidogrel is not licensed for this patient group; MI will be divided into STEMI and NSTEMI and unstable angina has replaced 'other vascular events'.

4.2 Overall aims and objectives of assessment

The purpose of the review is to assess the clinical and cost-effectiveness evidence describing the use of clopidogrel and MRD (+ASA or alone) in the prevention of OVEs in patients with history of MI, IS or TIA, or established PAD. Evidence relevant to the effectiveness of clopidogrel in patients with MVD will also be considered. This review is an update and focuses on relevant clinical and cost-effectiveness evidence that has become available since publication of TA90.[23]

5 ASSESSMENT OF CLINICAL EFFECTIVENESS

5.1 Methods for reviewing effectiveness

Methods for reviewing clinical and cost-effectiveness evidence are described in this section.

Search strategies

This review is an update of an existing review.[3] Consequently, the start date for searches of electronic databases is 2003. In addition to searching the two MS[50, 51] for relevant references, the following databases were searched for trials of clopidogrel and MRD:

Embase (2003 to 2009 week 36)
Medline (2003 to 2009 August week 4)
Web of Science (2003 to 2009)
The Cochrane Library (2003 to 2009 Issue 3)

The results were entered into an Endnote X2 library and the references were de-duplicated. Full details of the search strategies are presented in Appendix 1.

5.1.1 Inclusion and exclusion criteria

Two reviewers (JG/RD) independently screened all titles and abstracts. Full paper manuscripts of any titles/abstracts that were considered relevant by either reviewer were obtained where possible. The relevance of each study was assessed (JG/JO) according to the criteria set out below. Studies that did not meet the criteria were excluded and their bibliographic details were listed alongside reasons for their exclusion. These are listed in Appendix 5. Any discrepancies were resolved by consensus and where necessary, a third reviewer was consulted.

Study design: Only RCTs were included in the assessment of clinical effectiveness. Full EEs were included in the assessment of cost effectiveness.

The AG also identified and assessed the quality of existing SRs in order to cross check for the identification of additional studies as well as to gain an understanding of the issues related to the combining of data in this complex area. A summary and critique of relevant SRs is presented in Appendix 3.

Interventions and comparators: The effectiveness of two antiplatelet agents, used within their licensed indications was assessed: (i) clopidogrel alone and (ii) MRD alone or in combination with ASA. Studies that compared clopidogrel alone, or MRD (alone or in combination with ASA) with ASA or, where appropriate, with each other, were included in the review. Trials in which clopidogrel was used as an adjunct to percutaneous coronary intervention were

excluded from the review. Trials in which clopidogrel was combined with ASA were also excluded as they were not within the remit of the scope.[14]

Patient populations: For clopidogrel, patients with a history of MI or IS or established PAD were included. Patients with ACS were not included, neither were those with atrial fibrillation. For MRD, patients with a history of IS or TIA were included.

Outcomes: Data on any of the following outcomes were included in the assessment of clinical effectiveness: MI; stroke; TIA; death; AEs including bleeding complications. No data relating to health-related quality of life (HRQoL) or unstable angina were identified. For the assessment of cost effectiveness, outcomes included incremental cost per life years gained (LYG) and incremental cost per quality adjusted life year (QALY) gained.

5.1.2 Data extraction strategy

Data relating to both study design and quality were extracted by two reviewers (JO/MB) into an Excel spreadsheet. The two reviewers cross-checked each other's extraction and a third independent reviewer (YD) checked for accuracy and was consulted in cases of disagreement. Where multiple publications of the same study were identified, data were extracted and reported as a single study.

5.1.3 Quality assessment strategy

The quality of clinical-effectiveness studies was assessed by two reviewers (MB/JO) and checked by a third reviewer (YD) according to criteria based on NHS CRD Report 4.[52] The quality of the cost-effectiveness studies was assessed by two reviewers (CMS/AB) according to a checklist updated from that developed by Drummond et al.[53] All relevant information is tabulated and summarised within the text of the report. Full details and results of the quality assessment strategy for clinical and cost-effectiveness studies are reported in Appendix 2.

5.1.4 Methods of data synthesis

Direct evidence

The results of (i) clinical and (ii) economic data extraction and quality assessment are summarised in structured tables and as a narrative description. The decision problem of interest to this review was made up of the following comparisons: i) clopidogrel versus ASA; ii) clopidogrel versus MRD alone; iii) clopidogrel versus MRD+ASA; iv) MRD+ASA versus ASA and iv) MRD alone versus ASA.

Indirect evidence

Due to the differences between trials in terms of interventions and comparators, indirect analysis (using a MTC methodology) was performed on a variety of outcomes. The methods and results of the MTC are reported in Section 5.3.

Additional analysis by the Assessment Group

Using data provided by the manufacturers of clopidogrel, the AG undertook subgroup analysis and explored the clinical effectiveness of clopidogrel in patients with MVD. The AG was also able to explore whether key outcome events are distributed evenly across the whole period of trial follow-up, or if there are particular time points when patients appear to be at greater risk.

5.2 Results

5.2.1 Quantity and quality of research available

A total of 4576 titles and abstracts were screened for inclusion in the review of clinical and cost-effectiveness evidence. The process of study selection is shown in

Figure 5-1.[54] The flowchart shows that the two studies identified in our updated searches were added to the two already identified in TA90.[23]

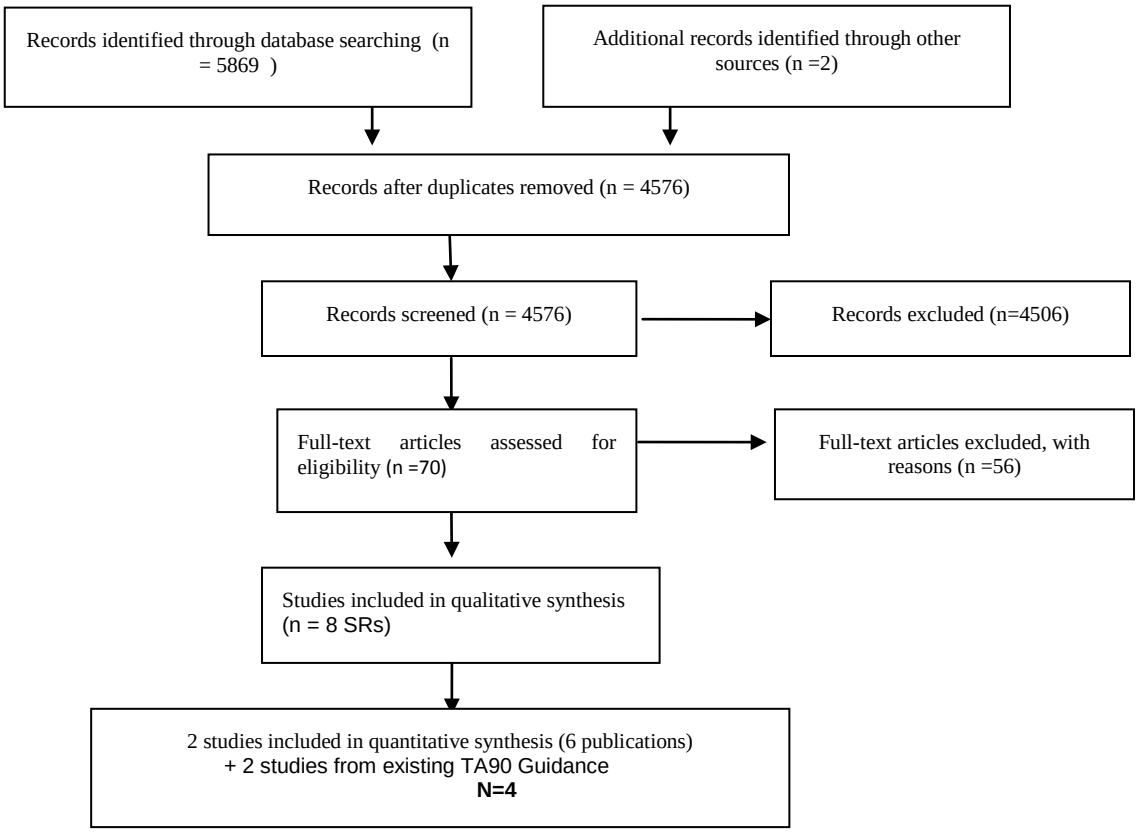

Figure 5-1 PRISMA Flowchart

5.2.2 Clinical effectiveness (RCTs)

Four RCTs, CAPRIE,[25] ESPS-2,[29] ESPRIT[55] and PRoFESS,[56] were reported in 28 publications and met the inclusion criteria for this review. These included the two trials[25, 29] (reported in 20 publications) that were used to inform the previous guidance.[23] The reference provided in the text refers to the primary report and any subsequent publications describing outcomes of the trials are listed by trial in Appendix 4.

The identified trials are summarised in Table 5-1. We did not include trials in which clopidogrel was combined with ASA as only clopidogrel alone was specified as an intervention or comparator in the scope issued by NICE.[14] This means that both MATCH[57] and CHARISMA[58] trials are excluded from the review. A full list of publications excluded following the application of the inclusion criteria is presented in Appendix 5.

In addition, six ongoing trials were identified; these are described in Appendix 6. However, limited detail is available related to these studies and they are not considered in this review. It is however worthy of note that the majority of the ongoing trials include clopidogrel+ASA as a comparator.

Table 5-1 Identified randomised controlled trials

Trial	Study design	Patients	Comparators
CAPRIE[25] 1996	Double-blind, placebo-controlled trial	19,185 patients with atherosclerotic vascular diseases manifested as either IS, MI or symptomatic PAD	CLOP (75mg/day) vs ASA (325 mg/day)
ESPS-2[29] 1996	Double-blind, placebo-controlled trial (2x2 factorial)	6,602 patients with prior stroke or TIA	ASA (50 mg/day) vs MRD (400mg/day) vs ASA (50mg/day) +MRD (400mg/day) vs placebo
ESPRIT[55] 2006	Open-label trial	2,736 patients with prior TIA or stroke*	ASA (30-325 mg/day) vs MRD (400mg/day)+ASA
PRoFESS[56] 2008	Double-blind trial	20,332 patients with prior stroke	MRD (400mg/day)+ASA (25mg/day) vs CLOP (75mg/day)

ASA=aspirin; MI=myocardial infarction; MRD=modified-release dipyridamole; PAD=peripheral arterial disease; RCT= randomised controlled trial; TIA=transient ischaemic attack; IS=ischaemic stroke; CLOP=clopidogrel
* 2763 were randomised but 24 patients excluded due to incomplete data, thus results are based on 2739 patients

Quality assessment of included RCTs

All of the included RCTs were of good quality (Appendix 2). Robust randomisation procedures were employed and baseline comparability between treatment groups was achieved. The use of blinding procedures was reported where appropriate and intention to treat (ITT) analyses were conducted for each trial. There was no evidence of selective reporting of outcomes in any of the trials.

Trial characteristics

The key characteristics of the included trials are summarised in Table 5-2. Of the four trials, three were double-blind and one was an open-label study (ESPRIT[55]). The majority of trials were conducted globally, whilst the participating centres in ESPS-2[29] were only located in Europe. All trials included patients with IS as a qualifying event and two included patients with a qualifying event of TIA.[29, 55] Only CAPRIE[25] included patients with MI or PAD. The trial sizes ranged from 2,763 to 20,332. Mean length of follow-up ranged between 1.91 and 3.5 years. Three trials were industry-funded whilst ESPRIT[55] was funded from a variety of non-industry sources. Two trials (CAPRIE,[25] ESPRIT[55]) utilised a composite as a primary endpoint, the components of which differed between the trials. In ESPS-2[29] three discrete primary endpoints were reported, whilst PRoFESS[56] reported on a single primary endpoint of recurrent stroke. Across the four trials, ASA dosage ranged from 50 mg per day (ESPS-2[29] and PRoFESS[56]) to 30-325 mg per day in ESPRIT[55] and 325mg per day in CAPRIE.[25]

Table 5-2 Summary of included trial characteristics

Trial name and comparators	Study design	No patients (N) Location	Qualifying events No pts (n)	Follow-up (mean)	Trial support	Outcomes
CAPRIE[25] 1996 CLOP (75mg) vs ASA (325mg)	Double-blind, placebo-controlled	N=19,185 Austria, Australia, Canada, Belguim, France, Finland, Germany, Italy, Netherlands, New Zealand, Portugal, Spain, Sweden, Switzerland, UK, USA	IS (n=6431) MI (n=6302) PAD (n=6452)	1·91 years (Range = 1-3 years)	Sanofi-aventis and Bristol-Myers Squib	Primary First occurrence of IS, MI, or vascular death Secondary First occurrence of IS, MI, amputation, or vascular death; vascular death; overall net benefit: any stroke (includes primary intracranial haemorrhage), MI or death from any cause; death from any cause
ESPS-2[29] 1996 ASA (50mg) vs MRD vs ASA (50mg) MRD+ASA vs placebo	Double-blind, placebo-controlled (2x2 factorial)	N=6,602 Austria, Belguim, France, Germany, Ireland, Italy, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, UK	TIA (n=1562) IS (n=5038)	2 years	Boehringer- Ingelheim	Primary Stroke; all cause death; stroke and/or all cause death Secondary TIA; MI; IS events (stroke and/or MI, and/or sudden death of thrombotic origin); other vascular events (pulmonary embolism, deep venous thrombosis, peripheral arterial occlusion, venous retinal thrombosis or combination of these events)
ESPRIT[55] 2006 ASA (30 to 325mg) vs MRD+ASA* (30 to 325 mg)	Open label	N= 2,736 Austria, Belguim, France, Germany, Italy, Netherlands, Portugal, Spain, Sweden, Switzerland, UK, Australia, China, Singapore, USA	TIA (n=920) Minor IS (n=1816)	3.5 years (SD 2.0)	Council of Singapore, European Commission; UK Stroke Association; French Ministry of Health; Netherlands: Janivo Foundation, AEGON N V; Heart Foundation; Thrombosis Foundation; University Medical Center Utrecht	Primary First occurrence of death from all vascular causes, non-fatal stroke, non-fatal MI, or major bleeding complication Secondary Death from all causes; death from all vascular causes and non-fatal stroke; all major ischaemic events (non-haemorrhagic death from vascular causes, non-fatal IS, or non-fatal MI); all vascular events (death from vascular causes, non-fatal stroke or non-fatal MI); major bleeding complications
PRoFESS**[56] 2008 MRD+ASA (50mg) vs CLOP (75mg)	Double-blind, non-inferiority	N=20,332 Argentina, Australia, Austria, Belgium, Brazil, Canada, China, Denmark, Finland, France, Germany, Greece, Hong Kong, India, Ireland, Israel, Italy,	Recent IS (n= 20,332)	2.5 years (range: 1.5–4.4)	Boehringer- Ingleheim. In selected countries also supported by Bayer Schering Pharma and GlaxoSmithKline.	Primary Recurrent stroke of any type Secondary Vascular events; first occurrence of stroke (non-fatal or fatal) or MI (non-fatal or fatal) or vascular death; first occurrence of stroke or

Trial name and comparators	Study design	No patients (N) Location	Qualifying events No pts (n)	Follow-up (mean)	Trial support	Outcomes
		Japan, Malaysia, Mexico, Netherlands, Norway, Portugal, Russia, Singapore, South Africa, South Korea, Spain, Sweden, Taiwan, Thailand, Turkey, Ukraine, UK, USA				major haemorrhagic event; death: IS, haemorrhagic stroke, stroke of uncertain cause, MI, haemorrhage excluding intracranial bleeding, other vascular causes, non-vascular causes life-threatening or non-life-threatening major haemorrhagic events; other designated vascular events; pulmonary embolism or retinal vascular accidents or deep vein thrombosis or peripheral arterial occlusion or TIA

ASA=aspirin; IS=ischaemic stroke; MI=myocardial infarction; MRD=modified-release dipyridamole; PAD=peripheral arterial disease; SD= standard deviation; TIA=transitory ischaemic attack; UK=United Kingdom; USA=United States of America; CLOP=clopidogrel *13% pts received immediate release dipyridamole

Patient characteristics

The key characteristics of patients in the included trials are summarised in Table 5-3. The mean age of the patients was similar across trials. The percentage of males appears to be greatest in CAPRIE.[25] PRoFESS[56] included the greatest proportion of patients with hypertension and DM. None of the trials characterised the patient population in terms of the number of affected vascular beds, so the number of patients per trial with MVD is unknown. However, the history of vascular events for the whole cohort of patients is reported for each trial; these are described in the right-hand column of Table 5-3. Compared to the other trials, in ESPS-2[29] there was a higher percentage of patients with PAD in addition to the qualifying event of IS/TIA. With the exception of CAPRIE[25] the modified Rankin Scale[59] was used as a measure of patient disability; this scale is widely used as an outcome measure for stroke in clinical trials. The scale ranges from 0-6, where 0 indicates no disability and 6 is death. All patients in ESPRIT[55] were rated as between 0 and 3, with 43% having no disability.

Table 5-3 Patient characteristics

Trial name/ comparators	Mean age (SD)	Gender (male) (%)	Modified Rankin Scale status (%)	Other factors (%)	% patients with history of vascular events
CAPRIE[25] (CLOP vs ASA)	62.5 years (11.1)	72	NS	Current smoker: 29.5 Ex-smoker: 49 Hypertension: 51.5 DM: 20	MI: 16.5 IS: 9 Intermittent claudication: 4.5 TIA/RIND: 10
ESPS-2[29] (ASA vs MRD vs MRD+ASA vs placebo)	66.7 years	58	0+1+2=69.1 3=14.2 4+5=16.6	Current smoker: 24 Hypertension: 60.5 DM: 15.3	PAD: 22
ESPRIT[55] (ASA vs MRD+ASA)	63 years (11)	66	0=43 1=33 2=18 3=6	Current smoker: 36.5 Hypertension: 59.5 DM: 18.5	MI: 7 Intermittent claudication: 5 Stroke: 11.5
PRoFESS[56] (MRD+ASA vs CLOP)	66.1 years (8.6)	64	0=14 1=37 2=25 3=14 4+5=9	Current smoker: 21 Ex-smoker: 36 Never smoker: 42.6 Hypertension: 74 DM: 28	MI: 7 TIA: 8.7 PAD: 3 Stroke: 18.25

ASA=aspirin; CLOP=clopidogrel; DM=diabetes mellitus; IS=ischaemic stroke; MI=myocardial infarction; MRD=modified-release dipyridamole; PAD=peripheral arterial disease; SD= standard deviation; RIND= reversible ischaemic neurologic disease; TIA=transitory ischaemic attack

CAPRIE

The key outcomes of the CAPRIE[25] trial are described in Table 5-4. For the whole trial population, statistically significant outcomes in favour of clopidogrel were noted for the primary outcome (first occurrence of IS, MI, or vascular death). The relative risk reduction was 8.7% in favour of clopidogrel (95% CI: 0.3 to 16.5; p=0.043). It has been noted[3] elsewhere that the point estimate favoured clopidogrel but this benefit appeared to be very small; the boundaries of the confidence intervals raise the possibility that clopidogrel is not more beneficial than ASA. A statistically significant risk reduction (23.8%) in favour of

clopidogrel was reported for the subgroup of patients with PAD (95% CI: 8.9 to 36.2; p=0.0028); however, the trial was not powered to detect differences between patient subgroups and so the finding should be interpreted with caution. No statistically significant differences between clopidogrel and ASA were noted for the subgroup of patients with IS or MI.

Table 5-4 Key outcomes of CAPRIE trial

CAPRIE[25] trial			
Outcomes	**Event rate per year CLOP (%)**	**Event rate per year ASA (%)**	**Relative risk reduction (%) (95% CI)**
Primary First occurrence of IS, MI, or vascular death	All patients: 5.32 Stroke subgroup: 7.15 MI subgroup: 5.03 PAD subgroup: 3.71	All patients: 5.83 Stroke subgroup: 7.71 MI subgroup: 4.84 PAD subgroup: 4.86	All patients: 8.7 (0.3 to 16.5) p=0.043 Stroke subgroup: 7.3 (-5.7 to 18.7) p=0.26 MI subgroup: -3.7 (-22.1 to 12) p=0.66 PAD subgroup: 23.8 (8.9 to 36.2) p=0.0028
Secondary First occurrence of IS, MI, amputation, or vascular death	All patients: 5.56	All patients: 6.01	All patients: 7.6 (-0.8 to 15.3) p=0.076
Vascular death	All patients: 1.90	All patients: 2.06	All patients: 7.6 (-6.9 to 20.1) p=0.29
Overall net benefit*	All patients: 6.43	All patients: 6.90	All patients: 7.0 (-0.9 to 14.2) p=0.081
Death from any cause	All patients: 3.05	All patients: 3.11	All patients: 2.2 (-9.9 to 12.9), p=0.71

CLOP=clopidogrel; ASA=aspirin; CI=confidence interval; IS=ischaemic stroke; MI=myocardial infarction; PAD=peripheral arterial disease; * any stroke (includes primary intracranial haemorrhage) MI or death from any cause, fatal bleeding

ESPS-2

Table 5-5 shows the key outcomes of ESPS-2.[3, 29] On the first primary outcome of stroke, statistically significant differences in favour of MRD+ASA were observed for two comparisons: MRD+ASA vs ASA (RR 0.76; 95% CI: 0.63 to 0.93) and MRD+ASA vs MRD alone (RR 0.75; 95% CI: 0.61 to 0.91). No difference was observed for the MRD vs ASA comparison. No other primary outcome (all cause death; stroke and/or all cause death) showed statistically significant differences between any two treatment arms.

Of the secondary outcomes, stroke/TIA, other vascular event, ischaemic events and vascular events, statistically significant differences were recorded in favour of MRD+ASA when compared with ASA (RR 0.80; 95% CI: 0.70 to 0.92), (RR 0.55; 95% CI: 0.33 to 0.94), (RR 0.77; 95% CI: 0.65 to 0.92), (RR 0.78; 95% CI: 0.67 to 0.91) respectively.

Of the secondary outcomes of TIA, stroke/TIA, ischaemic events and vascular events, statistically significant differences in favour of MRD+ASA compared to MRD alone were

noted (RR 0.80; 95% CI: 0.66 to 0.97), (RR 0.78; 95% CI: 0.69 to 0.90), (RR 0.76; 95% CI: 0.64 to 0.90), (RR 0.76; 95% CI: 0.65 to 0.89) respectively.

Table 5-5 Key outcomes of ESPS-2

Outcomes	Total events MRD n (%)	Total events MRD+ASA n (%)	Total events ASA n (%)	Relative risk (95% CI)
Primary				
MRD+ASA vs ASA				
Stroke		157 (9.5)	206 (12.5)	0.76 (0.63 to 0.93)
Stroke and/or death		286 (17.3)	330 (20.0)	0.87 (0.75 to 1.00)
All cause death		185 (11.2)	182 (11.0)	1.02 (0.84 to 1.23)
MRD+ASA v MRD				
Stroke	211 (12.8)	157 (9.5)		0.75 (0.61 to 0.91)
Stroke and/or death	321 (19.4)	286 (17.3)		0.89 (0.77 to 1.03)
All cause death	188 (11.4)	185 (11.2)		0.99 (0.81 to 1.19)
MRD vs ASA				
Stroke	211 (12.8)		206 (12.5)	1.02 (0.85 to 1.22)
Stroke and/or death	321 (19.4)		330 (20)	0.97 (0.85 to 1.11)
All cause death	188 (11.4)		182 (11.37)	1.03 (0.85 to 1.25)
Secondary				
MRD+ASA v ASA				
TIA		172 (10.4)	206 (12.5)	0.83 (0.69 to 1.01)
Stroke/TIA		18.1	22.6	0.80 (0.70 to 0.92)
MI		35 (2.1)	39 (2.4)	0.90 (0.57 to 1.41)
Other vascular event		21 (1.3)	38 (2.3)	0.55 (0.33 to 0.94)
Ischaemic events*		206 (12.5)	307 (16.1)	0.77 (0.65 to 0.92)
Vascular death		(7.1)	(7.2)	0.99 (0.77 to 1.27)
Vascular events		(14.9)	(19.0)	0.78 (0.67 to 0.91)
MRD+ASA v MRD				
TIA	215 (13.0)	172 (10.4)		0.80 (0.66 to 0.97)
Stroke/TIA	(23.1)	(18.1)		0.78 (0.69 to 0.90)
MI	48 (2.9)	35 (2.1)		0.73 (0.48 to 1.12)
Other vascular event	35 (2.1)	21 (1.3)		0.60 (0.35 to 1.03)
Ischaemic events*	271 (16.4)	206 (12.5)		0.76 (0.64 to 0.90)
Vascular death	(7.6)	(7.1)		0.94 (0.74 to 1.20)
MRD vs ASA				
TIA	215 (3.0)		206 (12.5)	1.04 (0.87 to 1.24)
Stroke/TIA	(23.1)		(22.6)	1.02 (0.90 to 1.16)
MI	48 (2.9)		39 (2.4)	1.23 (0.81 to 1.86)
Other vascular event	35 (2.1)		38 (2.3)	0.92 (0.58 to 1.45)
Ischaemic events*	271 (16.4)		266 (16.1)	1.02 (0.87 to 1.19)
Vascular death	(7.6)		(7.2)	1.06 (0.83 to 1.35)
Vascular events	(19.6)		(19.0)	1.03 (0.89 to 1.18)
MRD+ASA v MRD				
TIA	215 (13.0)	172 (10.4)		0.80 (0.66 to 0.97)
Stroke/TIA	(23.1)	(18.1)		0.78 (0.69 to 0.90)
MI	48 (2.9)	35 (2.1)		0.73 (0.48 to 1.12)
Other vascular event	35 (2.1)	21 (1.3)		0.60 (0.35 to 1.03)
Ischaemic events*	271 (16.4)	206 (12.5)		0.76 (0.64 to 0.90)
Vascular death	(7.6)	(7.1)		0.94 (0.74 to 1.20)
Vascular events	(19.6)	(14.9)		0.76 (0.65 to 0.89)

ASA=aspirin; CI=confidence interval; MI=myocardial infarction; MRD=modified-release dipyridamole; TIA=transient ischaemic attack

*All survival data are at 2 years

** stroke and/or MI, and/or sudden death of thrombotic origin

ESPRIT

The key outcomes of the ESPRIT[55] trial are described in Table 5-6. For the primary outcome of first occurrence of death from all vascular causes, non-fatal stroke, non-fatal MI, or major bleeding complication, the risk of event occurrence was statistically significantly lower in the MRD+ASA arm compared to the ASA arm (HR 0.80; 95% CI: 0.66 to 0.98).

For the secondary outcome of death from all vascular causes and non-fatal stroke, the rate of event occurrence was also statistically significantly lower in the MRD+ASA arm compared to the ASA arm (HR 0.78; 95% CI 0.62 to 0.97). This was also true for the outcome of all vascular events (HR 0.78; 95% CI: 0.63 to 0.97).

There were no statistically significant differences reported for any other outcome.

Table 5-6 Key outcomes of ESPRIT

ESPRIT[55] trial			
Outcomes	**Total events MRD+ASA n (%)**	**Total events ASA n (%)**	**Hazard ratio (95% CI)**
Primary			
First occurrence of death from all vascular causes, non-fatal stroke, non-fatal MI, or major bleeding complication	173 (12.69)	216 (15.20)	0.80 (0.66 to 0.98)
Secondary			
Death from all causes	93 (6.83)	107 (7.78)	0.88 (0.67 to 1.17)
Death from all vascular causes	44 (3.23)	60 (4.36)	0.75 (0.51 to 1.10)
Death from all vascular causes and non-fatal stroke	132 (9.69)	171 (12.42)	0.78 (0.62 to 0.97)
Major bleeding complications	35 (2.57)	53 (0.39)	0.67 (0.44 to 1.03)
Non-fatal extracranial	21 (1.54)	32 (2.32)	Not reported
Fatal extracranial	2 (0.15)	0	Not reported
Non-fatal intracranial	9 (0.66)	17 (12.21)	Not reported
Fatal intracranial	3 (0.22)	4 (0.29)	Not reported
Minor bleeding complications	171 (12.55)	168 (12.21)	Not reported
All major ischaemic events (non-haemorrhagic death from vascular causes, non-fatal IS, or non-fatal MI)	140 (10.27)	174 (12.65)	0.81 (0.65 to 1.01)
All vascular events (death from vascular causes, non-fatal stroke or non-fatal MI)	149 (10.93)	192 (13.95)	0.78 (0.63 to 0.97)
First IS	96 (7.0)	116 (8.43)	0.84 (0.54 to 1.10)
First cardiac event	43 (3.15)	60 (4.36)	0.73 (0.49 to 1.08)

ASA= aspirin; CI=confidence interval; IS=ischaemic stroke; MI=myocardial infarction; MRD= modified-release dipyridamole

PRoFESS

The key outcomes from the PRoFESS[56] trial are described in Table 5-7. Although the rate of recurrent stroke of any type was very similar in the MRD+ASA and clopidogrel groups (9% vs 8.8%, HR 1.01 [0.92 to 1.11]) the null hypothesis (that MRD+ASA is inferior to clopidogrel) could not be rejected as the predefined non- inferiority margin was -1.075.

For the secondary outcomes, the only statistically significant difference was in favour of MRD+ASA for the outcome of new or worsening congestive heart failure (CHF) HR 0.78 (95% CI: 0.62 to 0.96).

Table 5-7 Key outcomes of PRoFESS

PRoFESS[56] trial			
Outcomes	**Total events MRD+ASA (%)**	**Total events CLOP (%)**	**Hazard ratio for ASA+MRD (95% CI)**
Primary			
Recurrent stroke of any type	916 (9)	898 (8.8)	1.01 (0.92 to 1.11)
Secondary/tertiary			
Composite of vascular events (stroke, MI, or death from vascular causes)	1333 (13.1)	1333 (13.1)	0.99 (0.92 to 1.07)
MI	178 (1.7)	197 (1.9)	0.90 (0.73 to 1.10)
Death from vascular causes	435 (4.3)	459 (4.5)	0.94 (0.82 to 1.07)
Death from any cause	739 (7.3)	756 (7.4)	0.97 (0.87 to 1.07)
New or worsening CHF	144 (1.4)	182 (1.8)	0.78 (0.62 to 0.96)
Other vascular event	533 (5.1)	517 (5.1)	1.03 (0.91 to 1.16)
First IS	789 (7.7)	807 (7.9)	0.97 (0.88 to 1.07)
First recurrence of stroke or major haemorrhagic event	1194 (11.7)	1156 (11.4)	1.03 (0.95 to 1.11)
Major haemorrhagic event	419 (4.1)	365 (3.6)	1.15 (1.00 to 1.32)
Major haemorrhagic event: life-threatening	128 (1.3)	116 (1.1)	
Major haemorrhagic event: non life-threatening	291 (2.9)	249 (2.5)	
Haemorrhagic event (minor or major)	535 (5.3)	494 (4.9)	1.08 (0.96 to 1.22)
Intracranial haemorrhage	147 (1.4)	103 (1)	1.42 (1.11 to 1.83)
Intracerebral haemorrhage (haemorrhagic stroke)	90 (0.9)	55 (0.5)	
Haemorrhagic stroke - fatal	28 (0.3)	29 (0.3)	
Haemorrhagic stroke- non-fatal	62 (0.6)	26 (0.3)	
Intraocular haemorrhage	22 (0.2)	22 (0.2)	
Nonstroke intracranial haemorrhage	35 (0.3)	26 (0.3)	
Thrombotic thrombocytopenic or neutropenia	7 (0.1)	8 (0.1)	0.89 (0.32 to 2.44)

MI= myocardial infarction; CHF= congestive heart failure; HR= hazard ratio; CI= confidence interval; CLOP=clopidogrel MRD= modified-release dipyridamole; ASA= aspirin; IS= ischaemic stroke

Adverse events

Adverse events reported for each trial are described in Table 5-8. In ESPS-2[29] and CAPRIE[25] bleeding events in the trials were reported as secondary outcomes rather than as AEs. The reporting of AEs differed between trials. In CAPRIE[25]AEs were recorded as 'patients ever reporting,' in ESPS-2[29] as 'number of patients reporting at least one AE during the study'. In PRoFESS[56] only selected AEs leading to treatment discontinuation are presented in the published paper. Adverse events other than those related to bleeding were not reported for ESPRIT[55] (Table 5-6).

For CAPRIE,[25] patients in the clopidogrel arm were reported as experiencing significantly higher rates of rash and diarrhoea compared to the ASA arm. In the ASA arm, patients reported significantly more incidences of indigestion/nausea/vomiting and abnormal liver function. The numbers of patients experiencing gastrointestinal (GI) haemorrhage were greater in the ASA arm compared to clopidogrel, a result reported to be statistically significant. The rates of trial discontinuation due to AEs were similar in both arms of the trial.

In ESPS-2,[29] there was a significant difference between each arm in the occurrence of headaches. These appear to be greater in the arms where MRD was a feature of the treatment regimen. It is recorded in the published paper[29] that bleeding episodes were significantly more frequent and more often moderate or severe/fatal in treatment arms that included ASA. Any site bleeding was reported by 8.2% of patients in the ASA arm and 8.7% in the MRD+ASA arm, but was 4.7% and 4.5% in MRD alone and placebo groups. The rates of trial discontinuation due to AEs differed significantly, with higher rates reported in the two MRD arms than in the ASA or placebo arms.

Of the other reported AEs in ESPS-2,[29] GI events, vomiting, diarrhoea and headache were reported as being significantly different between treatment groups, but where the differences lie is unclear.[29]

In PRoFESS,[56] the rates of trial discontinuation were statistically significantly different between trial arms in favour of clopidogrel. Headache appears to be reported by many more patients in the MRD+ASA arm; an unsurprising outcome since MRD acts as a vasodilator.

Table 5-8 Adverse events reported for each trial

Trial name	Adverse event	CLOP n (%)	MRD+ASA n (%)	ASA n (%)	MRD n (%)	Placebo n (%)
CAPRIE[25a]	Rash*	578 (6.02)		442 (4.61)		
	Diarrhoea*	4 28 (4.46)		322 (3.36)		
	Indigestion/ nausea/vomiting*	1441 (15.01)		1686(17.59)		
	Abnormal liver function*	285 (2.97)		302 (3.15)		
	Any bleeding disorder	890 (9.27)		890 (9.28)		
	Intracranial haemorrhage	34 (0.35)		47 (0.49)		
	Gastrointestinal haemorrhage*	191(1.99)		255 (2.66)		
	Discontinuation due to AEs	(11.94)		(11.92)		
ESPS-2[29b]	Any AEs*		1056 (64)	990 (60)	1034 (62.57)	933 (56.58)
	GI event*		541 (32.80)	502 (30.44)	505 (30.53)	465 (28.20)
	Vomiting*		133 (8.06)	93 (5.64)	119 (7.19)	109 (6.61)
	Diarrhoea*		199 (12.06)	109 (6.6)	254 (15.36)	154 (9.33)
	Headache*		630 (38.18)	546 (33.11)	615 (37.18)	534 (32.38)
	Bleeding any site*		144 (8.73)	135 (8.19)	77 (4.66)	74 (4.49)
	Nausea		254 (15.39)	204 (12.37)	245 (14.81)	226 (13.71)
	Dyspepsia		290 (17.58)	283 (17.69)	274 (16.57)	266 (16.13)
	Gastric pain		274 (16.60)	242 (14.67)	240 (14.51)	219 (13.28)
	Mild bleeding		84 (5.09)	82 (5.01)	53 (3.20)	52 (3.15)
	Moderate bleeding		33 (2.0)	33 (2.0)	18 (1.09)	15 (0.91)
	Severe or fatal bleeding		27 (1.64)	20 (1.21)	6 (0.36)	7 (0.42)
	Dizziness		486 (29.47)	481 (29.16)	498 (30.10)	509 (30.88)
	Discontinuation due to AEs*		479 (29)	366 (22)	485 (29)	360 (21)
PRoFESS[56]	Headache	87 (0.9)	593 (5.9)			
	Vomiting	37 (0.4)	158 (1.6)			
	Nausea	58 (0.6)	155 (1.5)			
	Dizziness	52 (0.5)	134 (1.3)			
	Atrial fibrillation	143 (1.2)	122 (1.4)			
	Diarrhoea	42 (0.4)	102 (1.0)			
	Hypotension	35 (0.3)	54 (0.5)			
	Thrombotic thrombocytopenic or neutropenia	8 (0.1)	7 (0.1)			
	Patients with AEs leading to discontinuation*	1069 (10.6)	1650 (16.64)			

ASA= aspirin; MRD=modified-release dipyridamole; CLOP=clopidogrel; AE= adverse events; GI= gastrointestinal
*Reported as significant
a AEs categorised as patients ever reporting
b AEs were number patients reporting at least one AE during study
c Only selected AEs leading to treatment discontinuation are presented

5.2.3 Assessment Group analysis of time to first event rates

An important consideration in the analysis of trials in this area is the length of patient follow-up. It was noted earlier that the mean length of follow-up for the included trials ranged between 1.91 and 3.5 years (Table 5-2). The AG, using data from CAPRIE,[25] assessed the event rates over time for the outcome of IS in the IS only population of the trial (Figure 5-2 and Table 5-9) and the outcome of MI in the MI only population (Figure 5-3 and Table 5-10). The assessment indicates that patients appear to be at greatest risk of a recurrent event in the first six to twelve months; thereafter the risk decreases markedly. It is therefore important to explore how event rates change over time.

Figure 5-2 Trend in cumulative hazard for IS in the IS only population (CAPRIE)

Table 5-9 IS event rates in the IS only population at one, two and three years (CAPRIE)

	CLOP [redacted] ASA [redacted]	Person times at risk (years)	Number of IS events occurring within each year	Annual IS event rates (%)
Year 1				
	CLOP	[redacted]	[redacted]	[redacted]
	ASA	[redacted]	[redacted]	[redacted]
Year 2				
	CLOP	[redacted]	[redacted]	[redacted]
	ASA	[redacted]	[redacted]	[redacted]
Year 3				
	CLOP	[redacted]	[redacted]	[redacted]
	ASA	[redacted]	[redacted]	[redacted]
Overall				
	CLOP	[redacted]	[redacted]	[redacted]
	ASA	[redacted]	[redacted]	[redacted]

CLOP= clopidogrel; ASA= aspirin; IS= ischaemic stroke

Figure 5-3 Trend in cumulative hazard for MI in the MI only population (CAPRIE)

Table 5-10 MI event rates in the MI only population at one, two and three years (CAPRIE)

	CLOP (n=2845) ASA (n=2896)	Person times at risk (years)	Number of MI events occurring within each year	Annual MI event rates (%)
Year1				
	CLOP	[redacted]	[redacted]	[redacted]
	ASA	[redacted]	[redacted]	[redacted]
Year 2				
	CLOP	[redacted]	[redacted]	[redacted]
	ASA	[redacted]	[redacted]	[redacted]
Year 3				
	CLOP	[redacted]	[redacted]	[redacted]
	ASA	[redacted]	[redacted]	[redacted]
Overall				
	CLOP	[redacted]	[redacted]	[redacted]
	ASA	[redacted]	[redacted]	[redacted]

CLOP= clopidogrel; ASA= aspirin; MI= myocardial infarction

5.3 Methods for indirect synthesis

5.3.1 Justification for indirect analysis

The reported outcomes and their definitions varied significantly across the four trials (Table 5-11). For instance, in CAPRIE[25] data on first IS are available for the IS population but other outcomes are only available for the total population (i.e. IS, MI and PAD populations as a single group). The single common qualifying event in the four included trials[25, 29, 55, 56] was IS/TIA. Where appropriate, evidence synthesis, using a MTC approach, was undertaken using data from the IS/TIA overall populations[25, 29, 55, 56] or subpopulation.[25] The AG notes that the patient populations in the MTC are based on those described in the original trial publications and may therefore include patients with MVD.

Indirect comparison of common clinical outcomes (where available in at least two trials) was undertaken to estimate the relative efficacy between interventions in the IS/TIA populations.

Table 5-11 Outcomes reported by included RCTs for the IS/TIA population group

All outcomes reported (primary, secondary or tertiary)	CAPRIE[25]	ESPS-2[29]	ESPRIT[55]	PRoFESS[56]	No. of studies
First IS event (non-fatal or fatal)	X		X	X	3
Stroke (recurrent any type)		X		X	2
MI	X	X		X	3
Death from vascular cause	X		X	X	3
Death from all cause		X	X	X	3
Bleeding complications (major)			X	X	2
Bleeding complications (any)		X	X	X	3
First cardiac event (fatal and non-fatal MI, sudden death, cardiac death)			X		1
First event (IS, MI, or death from vascular cause)	X				1
First event (any stroke (includes primary intracranial haemorrhage), MI, fatal bleeding, or death from all cause)	X				1
First event (IS, MI, amputation, death from all vascular causes)	X				1
First event (non-fatal stroke, death from all vascular causes)			X		1
First event (non-fatal stroke, non-fatal MI, or major bleeding complication, death from all vascular causes)			X		1
First event (non-fatal stroke, non-fatal MI, or death from all vascular causes)			X		1
First event (stroke (non-fatal or fatal), MI (non-fatal or fatal), or death from all vascular causes)				X	1
First ischaemic event (stroke and/or MI, and/or sudden death of thrombotic origin)		X			1
First major ischaemic events (non-fatal IS, non-fatal MI, or non-haemorrhagic death from vascular causes)			X		1
Other vascular events (pulmonary embolism, retinal vascular accidents, deep vein thrombosis, peripheral arterial occlusion or TIA)				X	1
Other vascular events (pulmonary embolism, deep venous thrombosis, peripheral arterial occlusion, venous retinal thrombosis or combination of these events)		X			1
Stroke and/or death from all cause		X			1
TIA		X			1

IS=ischaemic stroke; MI=myocardial infarction; RCT=randomised controlled trial; TIA=transient ischaemic attack

5.3.2 Mixed treatment comparison

The relative treatment effects of clopidogrel, MRD+ASA, MRD alone and ASA ideally would have been derived from a single, direct, head-to-head RCT. However, such a trial does not exist. Instead, we have four trials[25, 29, 55, 56] assessing the treatment effects of a subset of the interventions of interest. A MTC is an alternative approach used to estimate relative treatment effects when the objective of the analysis is to compare more than two interventions. A MTC

is an explicit analytical framework and has been presented as an extension of standard meta-analysis by including multiple pair-wise comparisons across a range of different interventions.[60] The framework can then be used to derive a relative treatment effect of competing interventions in the absence of direct evidence.

The AG used a Bayesian approach to MTC to estimate the relative effectiveness measures for the interventions under comparison, ranking and making probability statements about the most effective intervention in a decision context. A fixed effect model was chosen for all analyses because random effect models failed to reach convergence. One possible reason for this failure could be the small number of trials (two to three trials in each analysis) and hence over-parameterisation.

A non-informative (flat prior) normal distribution was used for the log odds ratio (OR) of each relative comparison, thus the observed results are completely influenced by the data and not the choice of the priors. We estimated the relative effectiveness for each comparison using Markov Chain Monte Carlo (MCMC) for each analysis in WinBUGS version 1.4 statistical software (Medical Research Council Biostatistics Unit, Cambridge).[61] Two chains were used to ensure that model convergence was met after 100,000 iterations with a burn-in of 10,000 or more. Formal convergence of the models was assessed using trace plots and the Gelman Rubin approach.[62] Results are presented with summary statistics for RR and OR along with 95% CIs. Pair-wise ORs were estimated and converted to RRs using a standard approach. This was implemented in WinBUGS software by applying event rates across included trials from the reference comparator as the baseline probability (prob_baseline). Therefore, the RR=OR/ [(1−prob_baseline) + (prob_baseline*OR)]. The WinBUGS codes used in the analysis were adapted from the Multi-parameter Evidence Synthesis Research Group (MPES) and are presented in Appendix 7.

5.4 Results of MTC for IS/TIA population

All of the results presented in this section are related to IS/TIA populations only.

In this section, for clarity, the data analyses are presented in tables. For ease of reference, significant findings are emboldened in the tables. The networks relevant to each comparison are presented in Appendix 7.

It should be noted that the selection of the outcomes included in the MTC are driven by the available clinical data. In most analyses, the number of studies is small (two to three trials) and, although a large number of patients were included, the data used from the CAPRIE[25] trial were based on a subgroup of patients with IS. The findings of this MTC analysis should therefore be interpreted with caution.

5.4.1 Stroke

Data on recurrent stroke were available from four trials.[25, 29, 55, 56] However, due to differences in definition of 'recurrent stroke', analysis was performed separately for 'first IS' and 'any recurrent stoke'. The CAPRIE[25] trial did not report data on 'any recurrent stroke' and ESPS-2[29] trial did not present data on 'first IS'.

First ischaemic stroke

Three trials (CAPRIE,[25] ESPRIT[55] and PRoFESS[56]) provided direct head-to-head data on 'first IS'. Therefore it was possible to combine these trials through the MTC approach to calculate the relative efficacy of clopidogrel vs ASA, MRD+ASA vs ASA and MRD+ASA vs clopidogrel.

Table 5-12 shows head-to-head trial data and relative estimates calculated using the MTC analysis. The results show no major differences between the MTC results and head-to-head estimates from the included trials. Results from the MTC showed that no single estimated RRs were found to demonstrate a statistically significant difference between any pair of interventions. The observed RR for clopidogrel and MRD+ASA appeared to reflect a lower risk of 'first IS' compared to ASA. A RR of 0.968 was observed for MRD+ASA compared to clopidogrel. However, differences were not significant. There is no evidence to suggest that any intervention is superior to another in terms of prevention of 'first IS'.

Table 5-12 Relative risk for first IS in IS/TIA population (MTC)

	ASA		**CLOP**	**MRD+ASA**
CAPRIE[25]	[redacted]		[redacted]	
ESPRIT[55]	116/1376		--	96/1363
PRoFESS[56]			807/10151	789/10181
	Direct evidence from head-to-head trials		**Results from the MTC analysis**	
	Study	**RR* (95% CI)**	**RR* (95% CI)**	**OR (95% CI)**
CLOP vs ASA	CAPRIE[25]	[redacted]	[redacted]	0.915 (0.77 to 1.07)
MRD+ASA vs ASA	ESPRIT[55]	0.835 (0.64 to 1.08)	0.891 (0.75 to 1.04)	0.883 (0.74 to 1.04)
MRD+ASA vs CLOP	PRoFESS[56]	0.975 (0.88 to 1.07)	0.968 (0.88 to 1.05)	0.966 (0.87 to 1.06)

ASA= aspirin; CI=confidence interval; IS=ischaemic stroke; MRD= modified-release dipyridamole; MTC=mixed treatment comparison; OR=odds ratio; RR=relative risk; TIA= transient ischaemic attack; CLOP=clopidogrel *RR<1 is better than comparator; RR>1 is worse than comparator

Any recurrent stroke

Two trials (ESPS-2[29] and PRoFESS[56]) provided direct head-to-head data on recurrent stroke outcome. Therefore it was possible to combine these trials through the MTC approach to calculate the relative efficacy of MRD+ASA vs ASA, MRD alone vs ASA, MRD+ASA vs clopidogrel and MRD alone vs MRD+ASA. We were also able to estimate the indirect estimates from the MTC for clopidogrel vs ASA and MRD vs clopidogrel. Table 5-13 presents head-to-head trial data and results from the MTC analysis. No major differences in the MTC results and head-to-head estimates from the included trials were observed. Results from the MTC showed that clopidogrel and MRD+ASA were associated with fewer recurrent strokes relative to ASA. An increased risk of recurrent stroke was observed for MRD alone compared to clopidogrel or MRD+ASA. There was no difference between MRD alone compared to ASA, or between MRD+ASA and clopidogrel in terms of reducing recurrent stroke.

Table 5-13 Relative risk for any recurrent stroke in IS/TIA population (MTC)

	ASA	**CLOP**	**MRD+ASA**	**MRD**
ESPS-2[29]	206/1649		157/1650	211/1654
PRoFESS[56]		898/10151	916/10181	
	Direct evidence from head-to-head trials		**Results from the MTC analysis**	
	Study	***RR (95% CI)**	***RR (95% CI)**	**OR (95% CI)**
CLOP vs ASA	None	N/A	**0.752 (0.60 to 0.92)**	**0.727 (0.56 to 0.91)**
MRD+ASA vs ASA	ESPS-2[29]	**0.762 (0.62 to 0.92)**	**0.764 (0.62 to 0.92)**	**0.74 (0.59 to 0.91)**
MRD vs ASA	ESPS-2[29]	1.021 (0.85 to 1.22)	1.025 (0.85 to 1.21)	1.03 (0.83 to 1.25)
MRD+ASA vs CLOP	PRoFESS[56]	1.017 (0.93 to 1.1)	1.018 (0.93 to 1.11)	1.02 (0.92 to 1.12)
MRD vs CLOP	None	N/A	**1.376 (1.10 to 1.68)**	**1.431 (1.11 to 1.80)**
MRD vs MRD+ASA	ESPS-2[29]	**1.341 (1.10 to 1.62)**	**1.349 (1.10 to 1.61)**	**1.403 (1.12 to 1.73)**

ASA=aspirin; CI=confidence interval; MRD=modified-release dipyridamole; MTC=mixed treatment comparison; OR=odds ratio; RR=relative risk; CLOP=clopidogrel *RR<1 is better than comparator; RR>1 is worse than comparator

5.4.2 Myocardial infarction

Three RCTs (CAPRIE,[25] ESPS-2[29] and PRoFESS[56]) provided direct head-to-head data on MI outcome. It was possible to combine these trials through the MTC approach to calculate the relative efficacy of clopidogrel vs ASA, MRD+ASA vs ASA, MRD alone vs ASA, MRD+ASA vs clopidogrel and MRD alone vs MRD+ASA. We were also able to estimate the indirect estimates for MRD alone vs clopidogrel. Table 5-14 shows head-to-head trial data and estimates calculated using the MTC analysis. No major differences between the MTC results and head-to-head estimates from the included trials were observed. Results from the MTC, which are described in Table 5-14, showed that no single estimated RRs were found to

demonstrate a statistically significant difference between any pair of interventions in terms of prevention of MI events.

Table 5-14 Relative risk for myocardial infarction in IS/TIA population (MTC)

	ASA	CLOP	MRD+ASA	MRD
CAPRIE[25]	[redacted]	[redacted]		
ESPS-2[29]	39/1649		35/1650	48/1654
PRoFESS[56]		197/10151	178/10181	
	Direct evidence from head-to-head trials		**Results from MTC analysis**	
	Study	***RR (95% CI)**	***RR (95% CI)**	**OR (95% CI)**
CLOP vs ASA	CAPRIE[25]	[redacted]	[redacted]	1.098 (0.72 to 1.59)
MRD+ASA vs ASA	ESPS-2[29]	0.897 (0.57 to 1.40)	0.972 (0.65 to 1.38)	0.972 (0.65 to 1.39)
MRD vs ASA	ESPS-2[29]	1.227 (0.80 to 1.86)	1.291 (0.84 to 1.88)	1.302 (0.84 to 1.92)
MRD+ASA vs CLOP	PRoFESS[56]	0.901 (0.73 to 1.10)	0.893 (0.731 to 1.07)	0.892 (0.72 to 1.08)
MRD vs CLOP	None	N/A	1.208 (0.75 to 1.81)	1.215 (0.75 to 1.85)
MRD vs MRD+ASA	ESPS-2[29]	1.368 (0.89 to 2.10)	1.352 (0.883 to 1.98)	1.365 (0.88 to 2.02)

ASA=aspirin; CI=confidence interval; MRD=modified-release dipyridamole; MTC=mixed treatment comparison; OR= odds ratio; RR=relative risk; CLOP=clopidogrel *RR<1 is better than comparator; RR>1 is worse than comparator

5.4.3 Death from vascular causes

Three trials (CAPRIE,[25] ESPRIT[55] and PRoFESS[56]) provided direct head-to-head data on vascular death. Therefore it was possible to combine these trials through the MTC approach to calculate the relative efficacy of clopidogrel vs ASA, MRD+ASA vs ASA and MRD+ASA vs clopidogrel. Table 5-15 shows head-to-head trial data and estimates calculated using the MTC analysis. No major differences in the MTC results and head-to-head estimates from the included trials were noted. Results from the MTC showed no significant evidence to demonstrate differences in clopidogrel, MRD+ASA and ASA for vascular death outcome. There is no evidence to suggest that any intervention is superior to another in terms of prevention of vascular death.

Table 5-15 Relative risk for vascular death in IS/TIA population (MTC)

	ASA	CLOP	MRD+ASA	
CAPRIE[25]	[redacted]	[redacted]		
ESPRIT[55]	60/1376		44/1363	
PRoFESS[56]		459/10151	435/10181	
	Direct evidence from head-to-head trials		**Results from the MTC analysis**	
	Study	***RR (95% CI)**	***RR (95% CI)**	**OR (95% CI)**
CLOP vs ASA	CAPRIE[25]	[redacted]	[redacted]	0.827 (0.59 to 1.12)
MRD+ASA vs ASA	ESPRIT[55]	0.75 (0.51 to 1.01)	0.782 (0.57 to 1.04)	0.775 (0.56 to 1.04)
MRD+ASA vs CLOP	PRoFESS[56]	0.945 (0.83 to 1.07)	0.942 (0.82 to 1.06)	0.939 (0.82 to 1.06)

ASA=aspirin; CI=confidence interval; MRD=modified-release dipyridamole; MTC=mixed treatment comparison; OR= odds ratio; RR=relative risk; CLOP=clopidogrel *RR<1 is better than comparator; RR>1 is worse than comparator

5.4.4 Death from all causes

Three RCTs (ESPS-2,[29] ESPRIT[55] and PRoFESS[56]) provided direct head-to-head data on all-cause death. It was possible to combine these trials through the MTC approach to calculate the relative efficacy of MRD+ASA vs ASA, MRD alone vs ASA, MRD+ASA vs clopidogrel and MRD alone vs MRD+ASA. We also estimated the indirect estimates for clopidogrel vs ASA and MRD alone vs clopidogrel since no head-to-head data were available. Table 5-16 shows head-to-head trial data and estimates calculated using the MTC analysis. No major variation in the MTC results and head-to-head estimates from the included trials were observed. Results from the MTC showed that there was no evidence to demonstrate significant differences between clopidogrel, MRD+ASA, MRD and ASA for all-cause death.

Table 5-16 Relative risk of death from all causes in IS/TIA population (MTC)

	ASA	CLOP	MRD+ASA	MRD
ESPS-2[29]	182/1649		185/1650	188/1654
ESPRIT[55]	107/1376		93/1363	
PRoFESS[56]		756/10151	739/10181	
	Direct evidence from head-to-head trials		**Results from the MTC analysis**	
	Study	***RR (95% CI)**	***RR (95% CI)**	**OR (95% CI)**
CLOP vs ASA	None	N/A	0.992 (0.82 to 1.18)	0.992 (0.80 to 1.20)
MRD+ASA vs ASA	ESPS-2,[29] ESPRIT[55]	ESPS-2[29]: 1.016 (0.83 to 1.23) ESPRIT[55] 0.877 (0.67 to 1.14)	0.967 (0.82 to 1.12)	0.964 (0.80 to 1.14)
MRD vs ASA	ESPS-2[29]	1.03 (0.85 to 1.24)	1.007 (0.83 to 1.20)	1.01 (0.81 to 1.23)
MRD+ASA vs CLOP	PRoFESS[56]	0.975 (0.88 to 1.07)	0.976 (0.88 to 1.07)	0.974 (0.87 to 1.08)
MRD vs CLOP	None	N/A	1.021 (0.81 to 1.25)	1.024 (0.80 to 1.28)
MRD vs MRD+ASA	ESPS-2[29]	1.014 (0.83 to 1.22)	1.044 (0.86 to 1.24)	1.052 (0.85 to 1.28)

ASA=aspirin; CI=confidence interval; CLOP=clopidogrel; MRD=modified-release dipyridamole; MTC=mixed treatment comparison; OR= odds ratio; RR=relative risk; *RR<1 is better than comparator; RR>1 is worse than comparator

5.4.5 Bleeding

Data on bleeding were available from three RCTs (ESPS-2,[29] ESPRIT[55] and PRoFESS[56]). The CAPRIE[25] trial did not present bleeding data for patients in the IS subpopulation. As there was variation in bleeding reporting across trials, analysis was only possible for 'any bleeding' and 'major bleeding' as these were the common bleeding definitions used across trials.

Any bleeding

Three RCTs (ESPS-2,[29] ESPRIT[55] and PRoFESS[56]) provided direct head-to-head data on any bleeding. It was possible to combine these trials through the MTC approach to calculate the relative efficacy of MRD+ASA vs ASA, MRD alone vs ASA, MRD+ASA vs clopidogrel and MRD alone vs MRD+ASA. We also calculated the indirect estimates for clopidogrel vs ASA and MRD alone vs clopidogrel since no head-to-head data were available. The category of 'any bleeding' includes both minor and major bleeding. Minor events included haematuria, haematemesis, epistaxis, intraocular, purpura, gynaecological, internal and intracranial bleeding. Major bleeding included severe or fatal bleeding, life-threatening bleeding, intracranial bleeding, major haemorrhage, and major GI tract haemorrhage. Table 5-17 shows head-to-head trial data and estimates calculated using the MTC analysis. There were no major differences in the MTC results and head-to-head estimates from the included trials. Results from the MTC showed that MRD alone was associated with significantly fewer bleeding events compared to all comparators; the MRD vs clopidogrel estimates are based on indirect comparisons and are not supported by head-to-head trial data. There was no evidence to suggest any differences between clopidogrel vs ASA and MRD+ASA vs ASA for any bleeding.

Table 5-17 Relative risk for any bleeding in IS/TIA population (MTC)

	ASA	CLOP	MRD+ASA	MRD
ESPS-2[29]	135/1649		144/1650	77/1654
ESPRIT[55]	221/1376		206/1363	
PRoFESS[56]		494/10151	535/10181	
	Direct evidence from head-to head trials		**Results from the MTC analysis**	
	Study	***RR (95% CI)**	***RR (95% CI)**	**OR (95% CI)**
CLOP vs ASA	None	N/A	0.921 (0.75 to 1.10)	0.916 (0.74 to 1.11)
MRD+ASA vs ASA	ESPS-2[29] ESPRIT[55]	ESPS-2:[29] 1.066 (0.85 to 1.33); ESPRIT:[55] 0.941 (0.79 to 1.12)	0.991 (0.85 to 1.14)	0.991 (0.84 to 1.15)
MRD vs ASA	ESPS-2[29]	**0.569 (0.43 to 0.74)**	**0.549 (0.418 to 0.70)**	**0.529 (0.39 to 0.68)**
MRD+ASA vs CLOP	PRoFESS[56]	1.08 (0.95 to 1.21)	1.082 (0.958 to 1.21)	1.087 (0.95 to 1.23)
MRD vs CLOP	None	N/A	**0.593 (0.437 to 0.78)**	**0.582 (0.42 to 0.77)**
MRD vs MRD+ASA	ESPS-2[29]	**0.533 (0.40 to 0.69)**	**0.557 (0.425 to 0.71)**	**0.535 (0.40 to 0.69)**

ASA=aspirin; CI=confidence interval; MRD=modified-release dipyridamole; MTC=mixed treatment comparison; OR= odds ratio; RR=relative risk; CLOP=clopidogrel *RR<1 is better than comparator; RR>1 is worse than comparator

Major bleeding

Two RCTs (ESPRIT[55] and PRoFESS[56]) provided direct head-to-head data on major bleeding. It was possible to combine these trials through the MTC approach to calculate the relative efficacy of MRD+ASA vs ASA and MRD+ASA vs clopidogrel. We also estimated the indirect estimates for clopidogrel vs ASA since no head-to-head data were available. The category of 'major bleeding' included severe or fatal bleeding, life-threatening bleeding, intracranial bleeding, major haemorrhage, and major GI tract haemorrhage. Table 5-18 shows head-to-head trial data and estimates calculated using the MTC analysis. There were no major variations in the MTC results and head-to-head estimates from the included trials. Results from the MTC showed that clopidogrel was associated with significantly fewer bleeding events compared to ASA; these estimates are based on indirect comparisons and are not supported by head-to-head trial data. No statistically significant differences between MRD+ASA, clopidogrel and ASA in major bleeding events were observed.

Table 5-18 Relative risk for major bleeding in IS/TIA population (MTC)

	ASA	CLOP	MRD+ASA	
ESPRIT[55]	53/1376		35/1363	
PRoFESS[56]		365/10151	419/10181	
	Direct evidence from head-to-head trials		**Results from the MTC analysis**	
	Study	**RR (95% CI)**	**RR (95% CI)**	**OR (95% CI)**
CLOP vs ASA	None	N/A	**0.596 (0.36 to 0.89)**	**0.587 (0.35 to 0.89)**
MRD+ASA vs ASA	ESPRIT[55]	0.667 (0.43 to 1.01)	0.682 (0.433 to 1.008)	0.674 (0.42 to 1.00)
MRD+ASA vs CLOP	PRoFESS[56]	1.145 (0.99 to 1.31)	1.147 (0.99 to 1.31)	1.154 (0.99 to 1.32)

ASA= aspirin; CI= confidence interval; MRD= modified-release dipyridamole; MTC= mixed treatment comparison; OR= odds ratio; RR= relative risk; CLOP=clopidogrel *RR<1 is better than comparator; RR>1 is worse than comparator

5.5 Results of the MTC evidence for MI and PAD populations

Due to lack of available data, we were unable to carry out indirect analyses for the MI and PAD patient populations. Only CAPRIE[25] included patients with MI and PAD; data on these individual patients groups were not available from the other included studies.[29, 55, 56]

5.6 Summary of the evidence from the MTC

The MTC analysis was performed in patients categorised as having an IS/TIA as a qualifying event. The relative effectiveness of clopidogrel, MRD+ASA, MRD alone and ASA was evaluated based on evidence from four main RCTs[25, 29, 55, 56] that reported seven key clinical outcomes. The four trials included in the MTC analysis were: CAPRIE[25] (clopidogrel vs ASA); ESPS-2[29] (ASA vs MRD+ASA vs MRD alone vs placebo); ESPRIT[55] (MRD+ASA vs ASA); PRoFESS[56] (MRD+ASA vs clopidogrel). The clinically important outcomes that were included in the MTC exercise were: stroke (‘first IS’ and ‘any recurrent stroke’), MI, vascular death, death from all cause and bleeding (‘any bleeding’ and ‘major bleeding’). The selection of these outcomes was based on the availability of data from two or more of the four RCTs. One study (ESPS-2[29]) included a placebo arm and was included in the analysis but placebo results are not presented here. The reference comparator for all analyses was ASA. Results from the MTC showed that no single estimated RR was found to demonstrate a statistically important difference between any pair of interventions except for the outcomes of any recurrent stroke, ‘any ‘ and ‘major’ bleeding. The results further showed that MRD alone was statistically significantly associated with increased risk of any recurrent stroke compared to clopidogrel and MRD+ASA. However, it is worth noting that the findings from clopidogrel vs ASA and MRD alone vs clopidogrel were based on the indirect evidence and were not supported by any head-to-head data.

As detailed at the beginning of the section, caveats apply to the findings of our analysis due to the limited outcomes that were available for selection, the small number of trials and the use of data from subgroups from one trial.[25]

5.7 Patients with multivascular disease

The decision problem matrix (Table 4-1) described in the final scope[14] issued by NICE specified that if the evidence allows, the effectiveness of clopidogrel in people with MVD who are considered at high risk of recurrent OVEs should be considered. The AG notes that in the literature, there is a variety of definitions that characterise this population; this is an issue since the number of patients included in any MVD analysis will be affected by how the group is defined. The simplest and broadest definition of MVD described in the published literature is "patients with disease in more than one vascular bed". For completeness, the definitions identified by the AG from the literature are described in Table 5-19. Due to the apparent lack of consensus, the AG has derived a definition of MVD for the purposes of this document that appears to be consistent with the simplest and broadest definition described in the published literature.

Table 5-19 Definitions of MVD

MVD definition source	Definition of MVD
Bhatt 2006[21] (REACH registry)	Polyvascular disease was defined as coexistent symptomatic (clinically recognised) arterial disease in 2 or 3 territories (coronary, cerebral, and/or peripheral) within each patient
CAPRIE[25]	No formal definition of MVD was reported (not unusual at time of publication), however, subgroup analysis of 2144 patients with PAD/stroke and previous MI was presented
Ringleb 2004[63]	Patients with MVD are those with pre-existing symptomatic atherosclerotic disease from the overall CAPRIE population defined as having a self-reported history of IS and/or MI before the qualifying event for enrolment into the CAPRIE trial (NB Definition does not include PAD or TIA)
Sanofi-aventis/Bristol-Myers Squibb submission[51]	Patients with pre-existing symptomatic atherosclerotic disease (IS or MI) in addition to qualifying event (MS, pg 66) Patients with disease in more than one vascular bed (MS, pg 2)
AG's reclassification of populations in CAPRIE[25]	Patients with MVD defined as those who had experienced at least two of the following; CAD/MI, IS/TIA or PAD

IS=ischaemic stroke; TIA=transient ischaemic attack; MVD=multivascular disease; MI=myocardial infarction; PAD=peripheral arterial disease; AG=assessment group; CAD=coronary artery disease

Although the original CAPRIE[25] publication did not include a formal definition of MVD, the authors did present the results of a subgroup analysis of patients with PAD/stroke and previous MI. The findings support the view that patients with MVD are at greater risk of recurrent OVEs than patients with disease in a single vascular bed (Table 5-20).

Table 5-20 Risk of primary outcome event in patients with PAD/stroke and previous MI (CAPRIE)

Patient and treatment subgroup	IS, MI or vascular death		Relative risk reduction (95%CI)
	Events	Rate/year	
PAD/stroke with previous MI (n=2144)			
CLOP (nyrs 1963)	164	8.35%	22.7% (4.9 to 37.2)
ASA (nyrs 1825)	196	10.74%	

MI= myocardial infarction; CLOP= clopidogrel; PAD= peripheral arterial disease; CI= confidence interval; ASA= aspirin; nyrs= number of patient years at risk

5.7.1 Post-hoc analysis from the CAPRIE trial

One new publication[63] using data from the CAPRIE[25] trial was identified from the literature review. In this publication, patients with pre-existing symptomatic atherosclerotic disease from the overall CAPRIE[25] population were described in a subgroup analysis. As noted in Table 5-19 this was defined as a self-reported history of IS and/or MI before the qualifying event for enrolment in CAPRIE.[25] The data describing such events had been routinely collected in the case record forms. However, no standard procedures to validate such a pre-existing event were employed.[63] The AG notes that this subgroup of patients does not appear to include patients with PAD or TIA. The key outcomes of the analysis are described in Table 5-21. Compared with the overall population (n=19,185), the subgroup of patients with pre-existing symptomatic atherosclerotic disease which included IS or MI (n= 4,496) were found to have elevated event rates for the primary composite end point of IS, MI, or vascular death. The results favour clopidogrel over ASA at one year and three years on both the composite endpoints.

Table 5-21 Outcomes from CAPRIE MVD subgroup

CAPRIE[63] trial				
Outcomes	**Follow-up**	**Event rate CLOP (%) (n=2249)**	**Event rate ASA (%) (n=2247)**	**Relative risk reduction* (95% CI)**
First occurrence of IS, MI, or vascular death	1 year	8.8	10.2	14.9 (0.3 to 27.3) p=0.045
	3 years	20.4	23.8	
First occurrence of IS, rehospitalisation for ischaemia	1 year	16.1	18.5	12 0 (0.6 to 22.1) p= 0.039
	3 years	32.7	36.6	

ASA=aspirin; CI=confidence interval; IS=ischaemic stroke; MI=myocardial infarction; CLOP=clopidogrel
*RRR is not specifically related to a particular time point. It is an overall measure of how much the risk is reduced in the experimental group (clopidogrel) compared with the control group (ASA). This estimate is obtained from the Cox proportional-hazards model, which assumes that the hazard ratio is constant over time.

The authors[63] do not discuss the clinical effectiveness of clopidogrel on individual subpopulations (e.g. IS, MI or PAD) after removal of patients with MVD from the analysis. However, they do comment that the three-year composite event rate for the subpopulation without any pre-existing atherosclerotic disease is lower than that of the MVD group.

5.7.2 Assessment Group reclassification of patients from CAPRIE

Using the AG's definition of MVD (two of the following: CAD/MI, IS/TIA or PAD) and additional data provided by the manufacturer, the AG reclassified patients from CAPRIE[25] into those with atherosclerotic disease in a single vascular bed (described as 'MI only', 'IS only' or 'PAD only') and those who had disease in more than one vascular bed (e.g. patients who had experienced CAD/MI and an IS/TIA, or who had PAD and experienced a MI). The AG then compared the risk of two key outcomes (IS and MI) using the original CAPRIE[25] patient populations and the AG's reclassifications. The results are described in Table 5-22 (IS) and Table 5-23 (MI).

From Table 5-22 it can be seen that when the patients are reclassified, the risk of a future IS for individual patient groups is different in both treatment arms. The risk for IS only patients remains stable. The risk for the MVD subgroup is much greater than that of the MI and PAD patients.

Table 5-22 Changing risk of IS using AG reclassification of populations in CAPRIE

Patient group	**Original published IS rate % (n/N)**			**New* IS rate using additional data from manufacturers % (n/N)**			
Qualifying event	**CLOP**	**ASA**	**RR (95% CI)**	**AG Reclassif-ication**	**CLOP**	**ASA**	**RR (95% CI)**
IS	9.74 (315/3233)	10.57 (338/3198)	0.93 (0.80,1.07)	IS only	[redacted]	[redacted]	[redacted]
MI	1.34 (42/3143)	1.33 (42/3159)	1.01 (0.66,1.54)	MI only	[redacted]	[redacted]	[redacted]
PAD	2.51 (81/3223)	2.54 (82/3229)	0.99 (0.73,1.34)	PAD only	[redacted]	[redacted]	[redacted]
				MVD	[redacted]	[redacted]	[redacted]

IS=ischaemic stroke; MVD=multivascular disease; MI=myocardial infarction; PAD=peripheral arterial disease; CLOP=clopidogrel *After creating MVD population

From Table 5-23 it can be seen that when the patients are reclassified, the risk of a future MI for individual patient groups in both treatment arms is different. The risk for MI only patients remains stable. The risk for the MVD subgroup is greater than that of the IS and PAD patients.

Table 5-23 Changing risk of MI using AG reclassification of populations in CAPRIE

Patient group	Original published MI rate % (n/N)			New* MI rate using additional data from manufacturers % (n/N)			
Qualifying event	**CLOP**	**ASA**	**RR (95% CI)**	**AG Reclassif-ication**	**Clop**	**ASA**	**RR (95% CI)**
IS	1.36 (44/3233)	1.59 (51/3198)	0.85 (0.57,1.27)	IS only	[redacted]	[redacted]	[redacted]
MI	5.19 (163/3143)	5.51 (174/3159)	0.93 (0.76,1.15)	MI only	[redacted]	[redacted]	[redacted]
PAD	2.11 (68/3223)	3.34 (108/3229)	0.61 (0.42,0.83)	PAD only	[redacted]	[redacted]	[redacted]
				MVD	[redacted]	[redacted]	[redacted]

IS=ischaemic stroke; TIA=transient ischaemic attack; MVD=multivascular disease; MI=myocardial infarction; PAD=peripheral arterial disease; CLOP= clopidogrel *After creating MVD population

These findings indicate that patients with MVD (as defined by the AG) constitute an important clinical subgroup. It should be noted that the AG had access to relevant data from the CAPRIE[25] trial only and we were therefore unable to conduct similar analyses for the other identified trials.

5.8 Summary of clinical evidence

For clarity, Table 5-24 describes the main clinical efficacy findings. The direct evidence from the four included RCTs[25, 29, 55, 56] is outlined along with the AG assessment of time to event rates, the indirect evidence from the MTC and the AG assessment of the evidence for the MVD population. The dearth of new evidence for the MI and PAD populations is notable.

Table 5-24 Summary of clinical evidence

Trial and population	Outcome	Finding
Direct evidence		
CAPRIE[25] MI, IS, PAD	First occurrence of IS, MI or vascular death	CLOP superior to ASA for overall population
ESPS-2[29] IS/TIA	Stroke	MRD+ASA superior to MRD alone and superior to ASA
ESPRIT[55] IS/TIA	First occurrence of death from all vascular causes, non-fatal stroke, non-fatal MI or major bleeding complication	MRD+ASA superior to ASA
PRoFESS[56]	Recurrent stroke	CLOP and MRD+ASA similar
Time to event rates		
CAPRIE[25] MI and IS	MI and IS	Recurrent events for patients with disease in a single vascular bed tend to occur within the first 6 to 12 months
Indirect evidence		
ESPS-2[29] and PRoFESS[56] IS/TIA	Recurrent stroke	CLOP and MRD+ASA superior to ASA
ESPS-2[29] and PRoFESS[56] IS/TIA	Recurrent stroke	MRD alone = increased risk compared to CLOP, MRD+ASA, ASA
ESPS-2 [29]and PRoFESS[56] IS/TIA	Any bleeding	MRD alone = least risk compared to ASA, CLOP, MRD+ASA
ESPS-2[29] and PRoFESS[56] IS/TIA	Major bleeding	CLOP superior to ASA
MVD subgroup		
CAPRIE[25] MI, IS, PAD	IS and MI	Patients with disease in more than one vascular bed are an important clinical subgroup at greater risk of recurrent OVEs than patients with disease in single vascular bed

CLOP=clopidogrel; ASA=aspirin; MI=myocardial infarction; IS=ischaemic stroke; TIA= transient ischaemic attack; PAD= peripheral arterial disease; MVD=multivascular disease

5.9 Discussion of clinical evidence

Direct clinical evidence available

The clinical evidence base supporting the previously published NICE guidance (TA90)[23] for the prevention of OVEs in patients with a prior history of such events and established PAD was constructed from two trials (CAPRIE[25] and ESPS-2[29]) relevant to the use of clopidogrel, MRD and ASA. Since publication of this guidance, two more relevant trials have been published (ESPRIT[55] and PRoFESS[56]). The evidence base underpinning this update of TA90[23] is therefore focussed on four RCTs.

Only CAPRIE[25] included patients with MI and PAD; the remaining three trials included just patients with IS/TIA. This means that the clinical evidence base for patients with MI and PAD (except for those with MVD) has not changed since publication of the TA90[23] guidance. Results from CAPRIE[25] indicated that clopidogrel was more effective than ASA in preventing

a composite of events comprising IS, MI, or vascular death; however the size of the benefit appeared to be small. A subgroup analysis indicated that for the subgroup of patients with PAD, there was a statistically significant benefit of clopidogrel compared to ASA; however, the trial was not powered to detect differences within subgroups and so the chances of a false negative finding are high. The AG notes that the CAPRIE[25] trial does not distinguish between patients with NSTEMI and STEMI as the trial was carried out and reported before this distinction was used to differentiate between patient pathways. However, this clearly inhibits the interpretation of the results for these clinically important subgroups of patients.

The manufacturer's positive response to the AG's request for more detailed analyses of the CAPRIE[25] trial, allowed the AG to conduct a new post-hoc subgroup analysis of patients with MVD (see section 5.6 for discussion) and explore changes in key event rates for four patient populations (MI, IS, PAD, MVD) instead of the original three (MI, IS, PAD).

For patients with IS/TIA, clinical data from two relevant trials (ESPRIT[55] and PRoFESS[56]) have become recently available in addition to data from ESPS-2[29] and CAPRIE.[25] Unfortunately PRoFESS[56] yielded inconclusive results as the trial did not meet the predefined criteria for non-inferiority but showed similar rates for the primary outcome of recurrent stroke (MRD+ASA vs clopidogrel). Consequently, there is no direct evidence to support the use of clopidogrel instead of MRD+ASA, or vice versa, for the IS/TIA population. ESPS-2[29] showed that MRD+ASA leads to statistically significant relative risk reductions for the primary outcome of stroke and a range of secondary outcomes compared to ASA and MRD alone.The ESPRIT[55] trial also demonstrated statistically significant risk reductions for MRD+ASA vs ASA (first occurrence of death from all vascular causes, non-fatal stroke, non-fatal MI or major bleeding complication; death from all vascular causes and non-fatal stroke; all vascular events). This means that the additional clinical evidence available from the publication of ESPRIT[55] supports the original findings of ESPS-2[29] that MRD+ASA is preferred to ASA across a range of key outcomes.

Key differences between the trials providing direct clinical evidence

All of the trials relevant to the decision problem were considered to be of good quality. However, the trials were disparate in terms of their design, patient populations, interventions and definition/reporting of outcomes (clinical and safety) which means it is difficult to compare outcomes across the trials or perform evidence synthesis with any confidence using only the summary data reported in the published studies.

Design: The mean length of follow-up between trials ranged between 1.91 years[25] and 3.5 years.[55] ESPS-2[29] was the only non-industry funded trial.

Population: Patients in ESPRIT[55] were randomised within six months of a minor IS/TIA whereas patients in ESPS-2[29] and PRoFESS[56] were randomised within three months of IS/TIA and minor IS respectively. A marked divergence was observed in the disability ratings (as measured by the Rankin scale[64]) between the stroke patients in the three trials[29, 55, 56] that exclusively included only IS/TIA patients. To illustrate, in the ESPRIT[55] trial, entry criteria limited the study patients to those who had suffered a minor TIA or a minor IS (43% of patients had no stroke symptoms, 53% had minor symptoms) whereas ESPS-2[29] (17%) and PRoFESS[56] (24%) included patients with severe stroke symptoms. The AG notes that none of the trials identified patients with MVD as being a clinically important subgroup.

Interventions: There was also disparity in the daily doses of ASA given in the trial: 'up to 350mg',[25] 30 to 325mg[55] and 50mg.[29] In the UK, the current standard dose of ASA is 75mg per day. However, since there appears to be little variation in the efficacy of doses higher than 75mg, there may be no impact on the main outcomes of the trials, although the bleeding risk may be increased with higher doses. The efficacy of lower doses of ASA (less than 75mg per day) is less well established compared to higher doses.[9, 65]

Outcomes: Firstly, none of the trials had the same primary outcome. Secondly, two trials utilised a composite event as a primary oucome.[25, 56] The use of composite events in clinical trials has been criticised in a number of papers[66, 67] and guidelines[66] for their use have been published. The guidelines[66] state that to be meaningful to clinicians, composite events should include components that are: similar in importance to patients, occur with similar frequency, and are affected to a similar degree by the intervention. When looking at the primary composite event used in CAPRIE,[25] IS or MI may not be considered as important to patients as death. In addition, there were many more patients with IS in CAPRIE[25] than there were MIs or vascular deaths. The primary composite event described in ESPRIT[55] included death from vascular causes, non-fatal stroke, non-fatal MI and non-fatal major bleeding, these outcomes be may not be considered similar by patients. Thirdly, it is difficult to summarise the findings related to AEs, as the classification of these outcomes differed across the trials; this was especially apparent for "bleeding events". However, upon investigation, the AG did not identify any unexpected AEs associated with any of the drugs; bleeding was associated with ASA and headache was associated with MRD.

Indirect clinical evidence available

As previously discussed, the availability of four good quality RCTs did not allow the comprehensive comparison of clinical and safety outcomes associated with the relevant interventions across the key populations of interest. In an effort to make best use of all available clinical information, the AG undertook a MTC and investigated outcomes, where possible, for the IS/TIA population. The AG concluded that there were no major differences

in the results of the MTC and the direct estimates from head-to-head trials. However, two of the five newly generated comparisons do yield statistically significant results: MRD alone was associated with an increased risk of recurrent stroke when compared with clopidogrel; clopidogrel was associated with fewer major bleeding events compared with ASA. Due to the small numbers of trials involved in the MTC and the forced selection of limited outcomes, caveats apply to the results. In addition, the findings were based on patient populations in which there is no differentiation between patients with vascular disease in a single bed and those with MVD. The results of the indirect analyses, although confirmatory of the direct results, must therefore be interpreted with caution.

Patients with multivascular disease

Recently published data from the REACH[51] registry attests to the view that patients with MVD are at increased risk of future OVEs when compared to patients with disease in one vascular bed. Based on the post-hoc analyses described by the manufacturer in the MS and the post-hoc analyses conducted by the AG there is also evidence from CAPRIE[25] to support the view that patients with MVD are an important clinical subgroup whose event risk profiles are different from other subgroups of patients. In summary, it appears that patients with MVD have elevated risks for more than one event (IS and MI); this is in contrast to the IS only and MI only subgroups who have been shown to have elevated risks for single events (for example, IS only patients have high risks of IS and MI only patients have high risks of MI).

Currently there is no NICE guidance available which identifies a specific treatment for a patient who has MVD and the Institute[23] has called for further research in this complex area:

> "Further research is recommended on the effectiveness of clopidogrel in people who are at high risk of recurrent OVEs... and in people who have recurrent events while taking recommended antiplatelet therapy".

Evidence from the CAPRIE[25] trial allows post-hoc exploration of the clinical effectiveness of clopidogrel for patients with MVD and offers a starting point for future discussions regarding appropriate clinical pathways for this subgroup of patients. Existing analyses are based on different definitions of MVD and consensus is required in order to ensure informed and consistent decision-making for patients with MVD.

Commentary on European Medicines Agency approval and guidelines/guidance issued by NICE

The AG notes that ASA is not licensed for use in patients with PAD; nor is clopidogrel licensed for use in patients with TIA. However, the AG's clinical experts are of the opinion

that in clinical practice in England and Wales ASA is routinely prescribed for patients with PAD and sometimes clopidogrel is prescribed for patients with TIA who cannot tolerate MRD or ASA.

The distinction between patients with NSTEMI and STEMI is now important as recently updated NICE guidelines[24] still state that patients diagnosed as NSTEMI who are at moderate to high risk of MI or death should be treated with clopidogrel+ASA for a period of 12 months after the most recent acute event and after 12 months treatment should revert to low-dose ASA. At present, there is no NICE guidance for patients diagnosed with STEMI although CG48[27] indicates that these patients should receive clopidogrel+ASA for 4weeks after the most recent event and thereafter revert to standard treatment, usually low-dose ASA. It is not clear how the recommendations in TA90[23] fit with the published guidelines as TA90[23] does not differentiate between patients with NSTEMI and STEMI.

6 ASSESSMENT OF COST EFFECTIVENESS

6.1 Introduction

There are three distinct elements to this section on cost effectiveness. Firstly, a critical appraisal of the existing economic evidence describing clopidogrel and MRD since the publication of the previous NICE guidance[23] (TA90) is presented. Secondly, a critique of the two economic models submitted by the manufacturers is described. Thirdly, the results of the AG's *de novo* economic evaluation are presented and summarised.

6.2 Review of existing cost-effectiveness studies

Full details of the search strategy and the methods for selecting evidence are presented in Section 5. Of 34 potentially relevant studies, eleven met the criteria for inclusion in the cost-effectiveness review; one study[68] was also included in the systematic review that informed the previous guidance.[23] Of the eleven included studies, seven[68-74] were published in full while four[75-78] were available only in abstract format. Most of the studies were of reasonable quality; however, more detail and focussed critique of the clinical effectiveness evidence used to inform the economic evaluations would have improved the quality of the studies (Appendix 2).

Characteristics of economic evaluations

Five[68, 70, 71, 73, 75] of the eleven studies included were described as cost-effectiveness analyses (CEAs) and six as cost-utility analyses (CUAs). The CEAs have used a range of health outcomes including life saved, events avoided, life years lived, time spent free of stroke recurrence or disability, and life expectancy. All of the CUAs have used QALYs as the main measure of health outcome. As presented in Table 6-1 seven studies[68, 70, 74-78] compared clopidogrel versus ASA; Karnon et al[72] compared clopidogrel for the first two years followed by ASA indefinitely versus ASA; Chen et al[71] compared clopidogrel+low-dose ASA versus ASA; Beard et al[69] compared MRD+ASA versus MRD single agent, low-dose ASA, clopidogrel or no treatment; Matchar et al[73] compared placebo versus ASA, ASA+MRD or clopidogrel.

Table 6-1 Characteristics of economic studies

Study	Source	Type of study	Interventions	Study population	Country	Time period	Industry/author affiliation
Annemans 2003[68]	Full text	CEA	CLOP vs ASA	Patients with MI, IS or PAD; mean age of 62.5 years	Belgium	2 years	The paper was supported by a grant from Sanofi-Synthelabo and Bristol-Myers Squibb
Beard 2004[69]	Full text	CUA	MRD+ASA versus: 1) MRD single agent 2) Low-dose ASA 3) CLOP 4) No treatment	Patients who survived an initial acute stroke; mean age of 70 years	UK	25 years	This project was supported with funding from Boehringer-Ingelheim
Berger 2008[70]	Full text	CEA	CLOP vs ASA	Patients with MI, IS or PAD	Germany	2 years	Supported by Aventis Pharma Deutschland
Chen 2009[71]	Full text	CEA	CLOP + low-dose ASA vs ASA	Patients with established cardiovascular disease	USA	Follow up of CHARISMA study[58] (28 months)	This project has been funded by grants from Sanofi (Paris, France) and Bristol-Myers Squibb (New York, NY)
Delea 2003[75]	Abstract	CEA	CLOP vs ASA	Population with recent IS, MI or diagnosed with PAD; subgroups of 55, 65 and 75 year olds	USA	Lifetime of patient	NR
Karnon 2005[72]	Full text	CUA	CLOP for two years followed by ASA indefinitely vs ASA	Population with recent IS, MI or PAD aged 60	UK	40 years	This study was supported by Sanofi-Synthelabo and Bristol-Myers Squibb
Matchar 2005[73]	Full text	CEA	Placebo vs: 1) ASA 2) ASA+MRD 3) CLOP	Population with previous IS or TIA aged 70 and with the characteristics of those patients in the Framingham population with first IS	USA	Lifetime of patient	Source of financial support: The Stroke Policy Model[79] was developed with support from the Agency for Health Care Research, Quality (1 R03 HS11746-01). The current application was developed while Drs Matchar, Samsa served as consultants to Boehringer Ingelheim
Schleinitz 2004[74]	Full text	CUA	CLOP vs ASA	Population with previous MI or stroke or diagnosed with PAD; mean age 63	USA	Lifetime of patient	Dr. Schleinitz was supported by an ambulatory care training grant from the Department of Veterans Affairs, a training grant from the Agency for Healthcare Research and Quality (AHRQ), and an NIH

Study	Source	Type of study	Interventions	Study population	Country	Time period	Industry/author affiliation
							BIRCWH grant (HD43447).
Palmer 2005[76]	Abstract	CUA	CLOP vs ASA	Population with previous IS or TIA occurred in the last 90 days (median 15 days)	Belgium, France, Switzerland and UK	18 months	NR
Stevenson 2008[77]	Abstract	CUA	CLOP vs ASA	Population with previous MI, who sustain an IS or PAD (high-risk patients)	UK	Lifetime of patient	NR
Van Hout 2003[78]	Abstract	CUA	CLOP vs ASA	Population with previous MI or stroke or diagnosed with PAD	Netherland	Lifetime of patient	NR

CLOP= clopidogrel; ASA=aspirin; CEA=cost-effectiveness analysis; CUA=cost-utility analysis; DP=Dipyridamole; IS=ischaemic stroke; MI=myocardial infarction; MRD=modified-release dipyridamole; PAD=peripheral arterial disease; TIA=transient ischaemic attack; NR= not reported

The study populations in the included studies were made up of patients with a history of CVD (MI, IS, TIA or PAD); this matches the populations described in the key clinical trials used to derive efficacy data. Only one study[77] explicitly considered patients with MVD. The mean age varied according to the trial source used, ranging from 60 to 70 years. Only four studies[69, 72, 76, 77] described a UK population. Most of the studies adopted a lifetime perspective; however four[68, 70, 71, 76] adopted a short-term perspective (e.g. duration of the clinical study follow-up).

Economic models

Only one of the included studies was not based on an economic model; Chen et al[71] performed an economic evaluation using data from the CHARISMA[58] trial without any survival projection beyond 28 months. Matchar et al[73] used an individual sampling model based on a model previously developed for the secondary prevention of stroke. Berger et al[70] adapted the model developed by Annemans et al[68] and Beard et al[69] based their model on the model developed by Cambers et al.[80] All relevant assumptions and extra information describing the models is summarised in Table 6-2.

Table 6-2 Description of economic models

Study	Type of model	Perspective	Model assumptions	
			Outcomes	**Costs and resource use**
Annemans 2003[68]	Markov model. Cycle length: 6 months	Belgian public health payer	• Risk of death from other causes was equal for CLOP and ASA • Risk of vascular death was included in the model separately, because it was assumed that over the 2 year study period both drugs affected only vascular death • Life-expectancy does not decrease further when a patient has more than one additional event • Adverse events were only included where a difference between CLOP and ASA was expected, based on pharmacological profiles, and where hospitalisation and intensive resource use would have been required • Concomitant medication continued unchanged for the duration of the analysis or until death and, in view of the small difference in concomitant medication profiles for patients receiving ASA or CLOP, an average of the two groups was used for all patients	• DRG derived costs for Belgium were from the year 1997, and were updated to 2002 using an inflation rate of 3% • The total cost of patient management was calculated by estimating the total of acute costs and follow-up costs per patient • Acute costs covered hospital admission, initial investigations, interventions, readmission for further interventions and inpatient rehabilitation • Follow-up costs comprised outpatient rehabilitation, GP/specialist visits, follow-up examinations, complications, nursing homes and home care
Beard 2004[69]	Model based on Chambers 1999[80] model. Markov model. Cycle length: 90 days	UK healthcare service	• Patients entering the model were assumed to have survived an initial acute stroke event • Patients who survived an initial acute episode would be considered suitable for treatment with an antiplatelet therapy • Patients had already received rehabilitation treatment for the initial stroke event prior to entering the model, and were being placed on standard long-term care, according to their level of permanent disability/functional status • Only adverse events associated with withdrawal from therapy are important to outcomes in the model	No assumptions made
Berger 2008[70]	Markov model adapted from Annemans.[68] Cycle length: 6 months	German third party payer	Two scenarios are compared: survival data based on Framingham database and on Saskatchewan databases	German cost data for acute and follow-up treatment of patients with MI, IS or PAD as published by Diener[81] were decreased by the included costs for CLOP treatment due to their separate consideration within this Markov model7
Chen 2009[71]	No model has been developed	US health-care system (payer)	NR	NR

Study	Type of model	Perspective	Model assumptions	
Delea 2003[75]	Markov model. Cycle length: NR	NR	NR	NR
Karnon 2005[72]	Markov model. Cycle length: 1 year	UK NHS Perspective	The model assumes patients receive lifelong therapy with CLOP or ASA	NR
Matchar 2005[73]	Individual sampling model based on the Duke Stroke Policy Model (DSPM)[79] for secondary stroke prevention. The model has been run 100 times	Health care provider	• All patients are assigned an initial Rankin score of one • The placebo group was assumed to follow the natural history of 70-year-olds with the characteristics of those patients in the Framingham population with first IS • For each antiplatelet group, the cost per month was increased by an estimated cost of antiplatelet medications • For each antiplatelet group, the risk of subsequent IS was reduced, using a risk ratio that was estimated from the randomised trials	NR
Schleinitz 2004[74]	Markov model. Time Cycle length: 1 month	Societal perspective	• When more than two events occurred, the Markov state that combined the two events with the lowest utility was used • Inclusion of the variable severity of stroke not included in the main trial which the model is based on • It is assumed that CLOP did not alter the distribution of severity, based on studies of other antiplatelet therapies • As CAPRIE[25] results were heterogeneous for the three subgroups, the estimates and 95% confidence intervals for the efficacy of CLOP for each subgroup rather than the primary study estimate has been used • The efficacy of CLOP in reducing haemorrhagic side effects was varied by a factor of 0.5 to 2	• The calculation of chronic care costs after survival of severe stroke or intracranial haemorrhage and other chronic conditions includes 20% of the chronic cost of the other condition to account for overlapping therapy
Palmer 2005[76]	Markov model. Cycle length: NR	NR	NR	NR
Stevenson 2008[77]	Markov model. Cycle length: NR	NR	NR	NR
Van Hout 2003[78]	Markov model. Cycle length: NR	NR	NR	NR

ASA=aspirin; BNF=British national formulary; DP=dipyridamole; IS=ischaemic stroke; MI=myocardial infarction; MRD=modified-release dipyridamole; PAD=peripheral arterial disease; TIA=transient ischaemic attack; NR=not reported

Cost data and cost sources

All of the studies stated the currency used; five of them also included the currency year which ranged from 2002 to 2007. Four studies used Euros, three used pound sterling and four used US dollars. The majority of the studies discussed cost items and provided useful definitions of costs. Drugs costs have been taken from a variety of different sources including local cost lists;[68] published literature;[70] BNF[69, 72] and web of pharmacy wholesale suppliers.[73, 74] Costs of acute events including hospitalisations and acute care have been taken from the trial based papers;[70, 72] Medicare DRG data;[73, 74] NHS Trust Financial Return data[69] and the published literature.[70, 77] Only three papers[75, 76, 78] do not state the sources of the cost data used. All papers but one[73] have mentioned a discount rate for costs as Table 6-3 shows.

Table 6-3 Cost data and cost data sources

Study	Cost items and cost data sources		Currency and currency year	Discount rate
Annemans 2003[68]	Ambulatory costs from INAMI tariff list for Belgium; AEs, unit costs from Belgian DRG; cost of CLOP and ASA from 'Répertoire Commenté des medicaments' Public Belgian costing		Euros/2002	3%
Beard 2004[69]	The model considered 3 specific areas of resource use. Hospitalisation costs from NHS Trust Financial Returns data; community-based resource costs were based on the Personal Social Services Research Unit Health and Social Care Costs; drugs costs from BNF 2002 prices		£/2002	6%
Berger 2008[70]	a) Acute events b) Follow-up costs c) Cost of drug	Costs from the literature excluding cost of CLOP	Euros/ NR	3%
Chen 2009[71]	Hospitalisations, physician costs, procedures, post-acute care and medications. Prices were obtained from price weights derived from comparable populations of US patients		US $/2007	3%
Delea 2003[75]	Antiplatelet therapy; inpatient and outpatient treatment of IS; long-term care for patients with disability: sources NR		US $/NR	3%*
Karnon 2005[72]	a) Hospitalisations, physician costs and procedures b) Post-acute care c) Cost of drug with 100% compliance d) Cost of qualifying events and costs of new MI. e) Cost of new stroke and stroke as qualifying event	a) Chambers et al 1999[80] and Tengs 2003[82] b) CAPRIE Steering committee[25] c) BNF for costs of drugs 44th edition d) Robinson et al 2005[83] e) Chambers et al 1999[80]	£/2002	6%
Matchar 2005[73]	Cost of events from Medicare claims data; cost of drugs from WEB of Pharmacy wholesale and Federal Supply Schedule		US $/NR	NR
Schleinitz 2004[74]	a) Cost of MI and IS b) Cost of AEs c) Annual care costs of stroke d) Annual care costs of AEs e) Cost of drugs	a) to d)Medicare diagnostic-related group data and literature and published literature e) Average U.S wholesale price for medications and based on prices negotiated by a large volume purchaser	US $/2002	3%
Palmer 2005[76]	NR	NR	Euros/NR	Local guidelines
Stevenson 2008[77]	NR	Literature review	£/NR	3.5%
Van Hout 2003[78]	NR	NR	Euros/NR	4%

AE=adverse events; ASA=aspirin; BNF=British national formulary; DP=dipyridamole; IS=ischaemic stroke; MI=myocardial infarction; MRD=modified-release dipyridamole; NR=not reported; PAD=peripheral arterial disease; NR= not reported; TIA=transient ischaemic attack; DRG= diagnosis-related groups
* not clearly stated if for both costs and benefits

Efficacy data and data sources

Only Palmer et al[76] and Stevenson et al[77] present data related to efficacy, the rest of the studies only point out that efficacy data are taken from a specific trial. Table 6-4 describes the information from the main trials used in each of the economic evaluations.

Health outcome data and data sources

Six of the economic evaluations used QALYs as the main measure of health outcome; other outcomes include life year saved (LYS) and life expectancy.

Only Matchar et al[73] have not discounted health outcomes. In the study by Delea et al[75] it is not clear if discounting has been applied to both costs and benefits. In the study by Palmer et al,[76] discounting was used but the discount rate is not explicitly stated. Health outcome information from the included studies is summarised in Table 6-4.

Table 6-4 Health outcome data and data sources

Study	Efficacy data	Efficacy data sources	Health outcomes	Health outcome data sources	Discount rate
Annemans 2003[68]	NR	CAPRIE[25] and Saskatchewan database. In and outpatient management derived from analysis of Belgian and international publications and official Belgian health statistics, and were validated by a group of 8 Belgian clinical experts	Cost per LYS; quantity of events; events avoided	CAPRIE trial[25] and Saskatchewan database	3%
Beard 2004[69]	NR	ESPS-2 study[29] for all treatments except CLOP where data came from CAPRIE.[25] Risks for acute stroke recurrence from year 3 to 5 from Oxford Community Stroke Project and >5 years risks assumed to rise with age	Life years lived; QALYs; time spent free of stroke recurrence or disability; avoided strokes; number of events	Original trials (CAPRIE[25] and ESPS-2[29]) and published literature	1.5%
Berger 2008[70]	NR	CAPRIE trial[25] and a Delphi panel to adapt efficacy data to Germany setting	Fatal and non-fatal strokes; LYS	CAPRIE study[25] and Delphi panel	3%
Chen 2009[71]	NR	CHARISMA[58] and Saskatchewan database	Lost life expectancy	CHARISMA trial[58] and Saskatchewan database	3%
Delea 2003[75]	NR	CAPRIE study[25]	Life expectancy	NR	3% *
Karnon 2005[72]	NR	UK observational studies CAPRIE trial[25] Government Actuary Department (1999-2000)	QALYs; number of events; life years gained	CAPRIE study;[25] Harvard utility database; Tengs et al;[82] Derdeyn et al;[84] Zeckhauser et al;[85] Haigh et al;[86] Lee et al;[87] Danese et al[88]	1.5%
Matchar 2005[73]	NR	Transition functions from Framingham study CAPRIE study;[25] ESPS-2 study[29]	QALYs	Duke Stroke Policy Model;[79] 'utilities were estimated from a large survey of patients at risk for major stroke' (no ref)	NR
Schleinitz 2004[74]	NR	Based on data from CAPRIE[25] and mortality data from life tables. Rate of TTP with CLOP from an observational study	QALYs	Published papers; CAPRIE study[25]	3%

Study	Efficacy data	Efficacy data sources	Health outcomes	Health outcome data sources	Discount rate
Palmer 2005[76]	a) RR increase of CLOP vs ASA: serious vascular events: 1.11 b) RR increase of ASA vs CLOP: Major bleedings: 1.12	a) 'Cochrane review' b) CAPRIE trial[25]	QALYs	NR	'discount rates were applied according to the local guidelines'
Stevenson 2008[77]	a) RR high risk patients vs single event patients: 1.81 b) RR clopidogrel vs ASA in high risk patients: Vascular death: 0.87 (95% CI 0.63 to1.19) NF IS: 0.83 (95% CI 0.60 to1.15) NF MI: 0.53 (95% CI 0.32 to 0.86)	a) and b) CAPRIE study[25]	QALYs	NR	3.5%
Van Hout 2003[78]	NR	CAPRIE study[25]	QALYs	CAPRIE study[25]	4%

ASA=aspirin; NR= not reported; BNF=British national formulary; NF= non-fatal; DP=dipyridamole; IS=ischaemic stroke; LYS=life year saved; MI=myocardial infarction; MRD=modified-release dipyridamole; NR=not reported; PAD=peripheral arterial disease; QALY= quality adjusted life year; RR=relative risk; TTP= thrombocytopenic purpura; TIA=transient ischaemic attack; *(not clearly stated if for both costs and benefits)

Cost-effectiveness ratios

The results of the CEAs are described in Table 6-5. In summary, Annemans et al[68] and Berger et al[70] conclude that, for the overall population (MI, IS and PAD), clopidogrel is cost effective compared to ASA with an ICER of €13,390 per QALY and €14,380 per LYS (scenario 1) or €18,790 per LYS (scenario 2). Chen et al[71] and Delea et al[75] show an ICER of $36,343 per LYS and a range of $40,204 to $49,107 per LYS respectively, concluding that clopidogrel is cost effective compared to ASA.

Schleinitz et al,[74] Palmer et al,[76] and Van Hout et al[78] conclude clopidogrel is cost effective when compared with ASA (Table 6-5); although Schleinitz et al[74] also conclude that the current evidence does not support increased efficacy of clopidogrel in MI patients. Stevenson et al[77] estimate the mean cost per QALY for clopidogrel compared with aspirin was £5443 in patients with a previous history of MI, who then sustain an IS or a PAD event.

The evaluation by Beard et al[69] concludes that MRD+ASA is a cost-effective option with an ICER below €5,000 per QALY when compared with ASA or MRD alone and it dominates when compared with clopidogrel or no treatment.

The study by Karnon et al[72] concludes that the comparison of clopidogrel followed by ASA versus ASA yields an ICER of £21,489 per QALY.

Matchar et al[73] show that placebo versus ASA and placebo versus MRD+ASA have similarly low ICERs; however placebo versus clopidogrel yields a high ICER with a low probability of being cost effective.

The majority of the trials have performed univariate SA and probabilistic sensitivity analysis (PSA). In general, the SAs show consistency around the ICER. All SAs are summarized in Appendix 8. Beard et al[69] state that their model is sensitive to the long term costs of very disabled patients. Matchar et al[73] conclude that although the simulations in their model can support the results shown, these are not sufficiently robust.

Table 6-5 Cost-effectiveness results

Study	Total costs	Total outcomes	Incremental cost effectiveness ratios	Conclusion
Annemans 2003[68]	a) Cost of CLOP patients: €12,612 per patient b) Cost of ASA patients: €11,753 per patient	Events in ASA group: 120.22 Events in CLOP group: 107.2	ICER CLOP vs ASA; €13,390/LYG	The findings of this CEA suggest that secondary treatment of MI, IS and PAD patients with CLOP adds approximately 43 to 114 life years per 1,000 patients compared with ASA (depending on discounting)
Beard 2004[69]	Primary analysis (per 1,000 patients): a) No treatment: €23,489,812 b) ASA: €23,242,692 c) MRD: €23,434,359 d) ASA-MRD: €23,308,578 e) CLOP: €24,247,730 Secondary analysis (life-time) a) No treatment: €37,757,950 b) ASA: €37,513,168 c) MRD: €37,662,152 d) ASA-MRD: €37,726,731 e) CLOP: €38,870032	Primary analysis (per 1,000 pts): a) No treatment: 2,357 QALYs b) ASA:2,370 QALYs c) MRD: 2,360 QALYs d) ASA-MRD: 2,385 QALYs e) CLOP: 2,374 QALYs Secondary analysis (life-time) a) No treatment: 4,199 QALYs b) ASA:4,248 QALYs c) MRD: 4,219 QALYs d) ASA-MRD: 4,306 QALYs e) CLOP: 4,265 QALYs	**5 and 25 years analysis:** • ASA+MRD vs ASA: ICER: £4,207-3,666/QALY • ASA+MRD vs MRD: ICER:dominated -£742.29/QALY • ASA+MRD vs CLOP: ICER: CLOP dominated • ASA+MRD vs no treatment: ICER: No treatment dominated	The current model suggests that, based on a consideration of first recurrence of stroke and the acute treatment impacts of TIAs and non-fatal OVEs, antiplatelet therapy based on MRD+ASA is a cost-effective treatment option over standard ASA. The model is sensitive to the long term costs of very disabled patients
Berger 2008[70]	Overall, the 2-year costs per 1000 patients under immediately initiated CLOP prophylaxis were calculated to be €1,241,440	ASA (events per 1,000 patients): • Vascular death: 33.12 • Non-fatal events: 87.09 • All vascular events: 120.22 CLOP: • Vascular death: 30.91 • Non-fatal events: 76.11 • All vascular events: 107.02	ICER: scenario 1: €14,380/LYS; scenario 2: €18,790/LYS;	The presented model shows cost-effectiveness of secondary prevention with CLOP vs ASA in patients with MI, IS or PAD

Study	Total costs	Total outcomes	Incremental cost effectiveness ratios	Conclusion
Chen 2009[71]	Mean cost per patient: ASA group; $11,136 CLOP+ASA group: $13,743	Life expectancy without in-trial events (years): Male, age 65: 11.63; Female, age 65: 13.17 Unadjusted lost life expectancy associated with specific in-trial events (years): Male, age 65=mild stroke: 6.23; moderate-severe stroke: 8.71; MI:4.69 Female, age 65=mild stroke: 7.53; moderate-severe stroke: 10.34; MI:5.93	• Overall population: ICER: $36,343 /LYG • Population aged<65: ICER: $28,144 /LYG • Population aged≥65: ICER: $/61,213LYG • Male population: ICER: $31,024/LYG • Female population: ICER: $54,817/LYG	For the pre-specified subgroup of CHARISMA[58] patients with established CV disease, adding CLOP to ASA for secondary prevention over 28 months of therapy appears to increase life expectancy modestly at a cost commonly considered acceptable within the US health-care system
Delea 2003[75]	NR	NR	ICER ranges from $40,204–$49,107 per life-year saved	CLOP is cost effective vs ASA in patients with recent IS, recent MI, or PAD
Karnon 2005[72]	Lifetime costs: ASA: £18,380,509 CLOP: £19,199,554	Total number of events: ASA: 195; CLOP: 172 Life years gained: ASA:14,199; CLOP:14,242 QALYs gained: ASA:11,964; CLOP:12,002	ICER: £21,489/QALY £18,888/LYG	CLOP has been demonstrated to be a cost-effective treatment in patients at risk of secondary OVEs, is clinically superior to ASA and has great potential for reducing the morbidity and mortality caused by these diseases
Matchar 2005[73]	Total cost per patient: Placebo group: $48,405 ASA group: $48,681 CLOP group: $52,721 MRD+ASA: $53,004	Total QALYs per patient: Placebo group: 3.54 ASA group: 3.70 Clopidogrel group: 3.77 MRD+ASA: 3.93	Based on the means for 100 runs of 10,000 patients each. • Placebo v. ASA: $1,725 /QALY • Placebo vs CLOP: $57,714/QALY • Placebo vs MRD+ASA: $1,769/QALY	ASA is superior to placebo. Choice between ASA and MRD+ASA is less obvious; but the more the decision maker is WTP for improved outcomes the more likely it is that MRD+ASA will be preferred. CLOP was seldom judged to be the optimal strategy. But, results were not sufficiently robust to select between MRD+ASA and ASA based on statistical considerations alone

Study	Total costs	Total outcomes	Incremental cost effectiveness ratios	Conclusion
Schleinitz 2004[74]	**CLOP:** PAD: $123,300; stroke: $201,400; MI: $98,500 **ASA:** PAD:$109,500; stroke: $196,000; MI: $91,700	**QALYs (CLOP):** PAD: 9.58; stroke: 8.66; MI: 10.83 **QALYs (ASA):** PAD: 9.03; stroke: 8.49; MI: 11.09	PAD: $25,100/QALY CLOP more effective STROKE: $31,200 /QALY CLOP more effective MI: -$26,200/QALY ASA more effective	CLOP provides a large increase in QALYs at a cost that is within traditional societal limits for patients with either PAD or a recent stroke. Current evidence does not support increased efficacy with CLOP vs ASA in patients after MI
Palmer 2005[76]	NR	NR	20,111€/QALY in Belgium 18,882€/QALY in France 15,620€/QALY in Switzerland 15,713€/QALY in UK	In the four countries the ICER falls below the acceptable thresholds, showing that CLOP compared to ASA is cost effective in the studied population
Stevenson 2008[77]	NR	NR	The mean cost per QALY for CLOP compared with ASA was £5,443 (95% confidence interval £2,332 to dominated)	The model suggests that, in patients with a previous MI event and a subsequent IS or PAD event, CLOP can be considered cost effective compared with ASA in terms of current UK thresholds
Van Hout 2003[78]	NR	NR	ICER: €17,279/QALY with event specific risk reductions and €15,776/QALY using constant RRR of 8.7%	CLOP shows as a dominant strategy in patients not eligible for treatment with ASA. The cost effectiveness is within an acceptable range when compared with ASA, especially in high-risk patients

ASA=aspirin; CLOP= clopidogrel; BNF=British national formulary; ICER=incremental cost-effectiveness ratio; LYG=life year gained; MRD=modified-release dipyridamole; NR= not reported; IS=ischaemic stroke; MI=myocardial infarction; NR=not reported; CV= cardiovascular; OVE=occlusive vascular events; PAD=peripheral arterial disease; QALY=quality adjusted life year; TIA=transient ischaemic attack; WTP=willingness to pay

Summary of evidence and discussion

In general, the results of the literature review of cost-effectiveness evidence, show that, from a health service perspective, the use of clopidogrel in patients with previous PAD, IS or MI is a cost-effective option compared with ASA in the secondary prevention of OVEs. However, it is noted that Schleinitz et al[74] conclude that current evidence does not support increased efficacy of clopidogrel in the MI patient group; this is the only evaluation which includes subgroup analysis to estimate ICERs by patients' previous event. This is also the only study not funded by a pharmaceutical manufacturer (four papers[75-78] did not provide details of industry affiliation).

The combination of MRD+ASA seems to be cost effective compared with any other treatment (vs ASA, vs CLOP, vs no treatment) in patients with previous IS or TIA in the secondary prevention of OVEs. There is only one evaluation[69] which includes this combination (MRD+ASA) and therefore the evidence base is limited.

Although model structures are similar, the length of the cycles differs from one study to another and the assumptions regarding the transition probabilities (e.g. Annemans et al[68] life expectancy assumptions) are not always reliable. Data in the models are from a broad variety of sources which makes it difficult to pool the results and make definitive conclusions.

All evaluations except three[70, 71, 77] were published prior to 2006; this means more recent trials and papers have not been used to inform the economic evaluations (e.g. clinical data from PRoFESS,[56] REACH,[15] or MATCH[57] are not described in the papers). The relevance of this cost-effectiveness review to decision making is therefore limited as the economic evaluations are not based on the most up-to-date clinical data.

6.2.1 Review of Boehringer-Ingelheim submission

Table 6-6 NICE reference case checklist

NICE reference case requirements	Reference case	Does the *de novo* economic evaluation match the reference case?
Defining the decision problem	The scope developed by the Institute	As per the final scope issued by NICE
Comparators	Therapies routinely used in the NHS, including technologies currently regarded as best practice	ASA, CLOP, MRD+ASA and no treatment
Perspective on costs	NHS and PSS	As per the final scope issued by NICE
Perspective on outcomes	All health effects on individuals	As per the final scope issued by NICE
Type of economic evaluation	Cost-effectiveness analysis	Cost-effectiveness analysis
Synthesis of evidence on outcomes	Based on a systematic review	All data are derived from head to head trials (mainly PRoFESS[56])
Measure of health benefits	QALYs	QALYs
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	EQ-5D used to collect data from patients in the PRoFESS[56] trial; published literature
Source of preference data for valuation of changes in HRQoL	Representative sample of general public	EQ-5D used to collect data from patients in the PRoFESS[56] trial; published literature
Discount rate	An annual rate of 3.5% on both costs and QALYs	3.5% per annum for costs and health effects
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	All QALYs estimated by the model have the same weight

ASA=aspirin; LY=life years; QALY=quality adjusted life years; CLOP=clopidogrel; NICE= national institute for clinical excellence' HRQoL= health related quality of life; PSS= personal social services; MRD= modified release dipyridamole

Overview of submitted manufacturer's submission

A Markov model was designed to assess the cost effectiveness of MRD+ASA vs ASA alone, clopidogrel and no treatment for the secondary prevention of OVEs in:

- Patients who have experienced an IS and are tolerant of ASA
- Patients who have experienced a TIA and are tolerant of ASA

The model is based on the model developed by the Technology Appraisal Group to inform the previous guidance.[3] The structure of the manufacturer's model is shown in Figure 6-1.

The model estimates costs from the perspective of the UK NHS, and health outcomes in terms of life years and QALYs in a simulated cohort of 1,000 patients initially aged 45–80 years using a time horizon of 2.5–50 years and a cycle length of six months.

Costs and benefits have been discounted at a rate of 3.5% per annum.

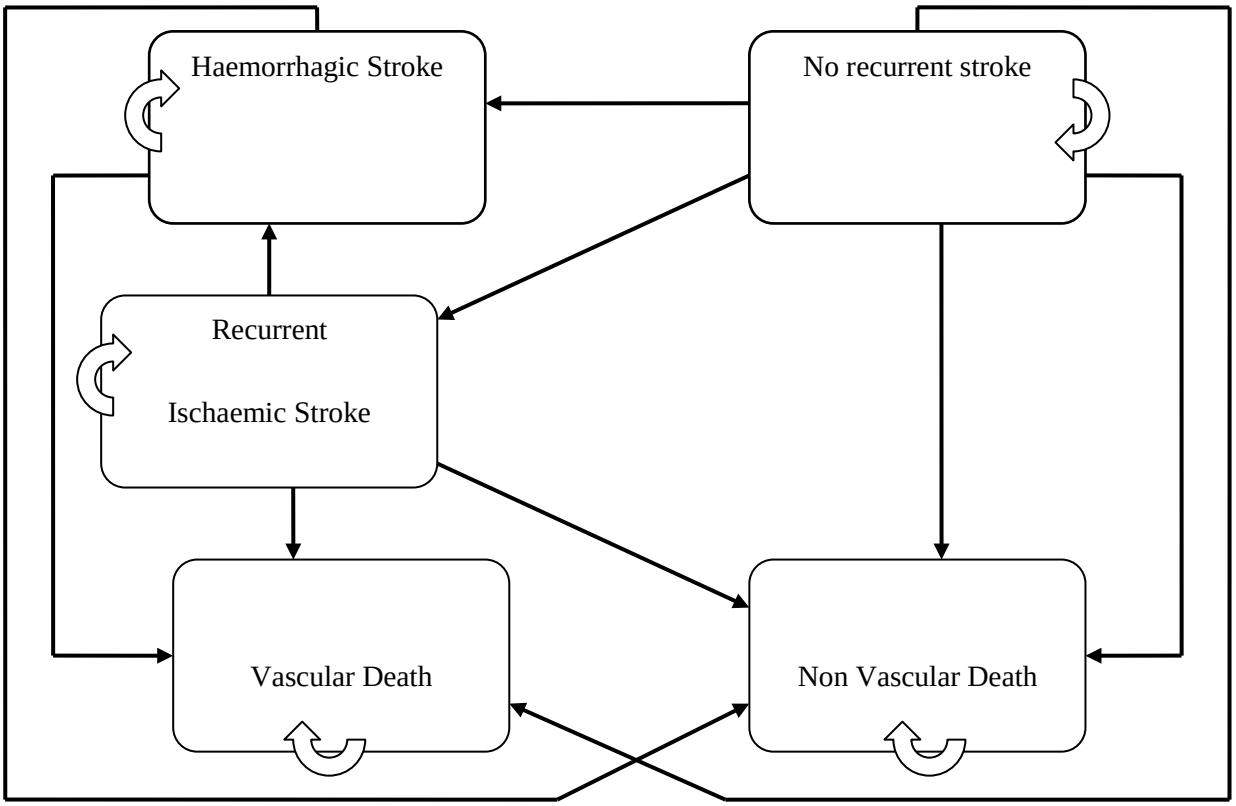

Figure 6-1Schematic structure of the Boehringer-Ingelheim model

The model presents five health states:

- No recurrent stroke
- Recurrent IS
- Haemorrhagic stroke
- Vascular death
- Non-vascular death

Patients enter into the model in the 'no recurrent stroke' health state, from where they may move to any other state or remain in the same state. From the 'recurrent IS' state patients may move to 'haemorrhagic stroke', 'vascular death' or 'non-vascular death', or remain in the 'recurrent IS' state. In the 'haemorrhagic stroke' state, patients will either remain in this state or die. Once patients enter the 'haemorrhagic stroke' health state, any additional recurrent haemorrhagic stroke events are not recognised in the model. The manufacturer states that this restriction is introduced to avoid the situation where an additional event (e.g. new IS) leads to a patient's utility state improving. If multiple events occur in a single cycle, one event is given priority in allocating patients to a health state in the following order of descending priority: death, haemorrhagic stroke, IS. The model also includes two tunnel health states: 'other haemorrhagic events' (OHEs) and 'new or worsening CHF'.

Summary of clinical effectiveness data

Transition probabilities during the first four years are derived from different trials for each of the arms:

- MRD+ASA and clopidogrel: PRoFESS[56] trial
- ASA alone: combination of ESPRIT[55] trial and ESPS-2[29] trial
- No treatment: ESPS-2[29] trial

Beyond the first four years, the transition probabilities are assumed to remain constant at the values of the last monthly cycle of the fourth year period for the following transitions:

- New recurrent IS from the 'no recurrent stroke' state
- Haemorrhagic stroke from the 'no recurrent stroke' state
- Haemorrhagic stroke from the 'new recurrent IS' state

The manufacturer used published data from the Oxfordshire Community Stroke Project[89] and the Lothian Stroke Registry[90] to estimate the overall death rate amongst stroke patients compared to the general population. A multiplier of 1.5 was used to generate an overall expected age-related death rate beyond the trial period from the Office of National Statistics (ONS) death rate data for the general population. The vascular and non-vascular death rates beyond the four years of the trial were assumed to sum to this rate.

The manufacturer has assumed that those patients who have experienced a TIA had a rate of previous IS events equal to 80% of those who had experienced a previous IS. This assumption is made on the basis of the previous MTA[3] in which the AG group made the same assumption.

Summary of costs and resource use

(i) Event costs

Separate costs were assigned to the health states of 'no recurrent stroke', 'recurrent IS' and 'haemorrhagic stroke' based on the estimated percentage of patients who were disabled in each health state. Data from the PRoFESS[56] trial were used to estimate the percentage of patients in each of these three health states who were disabled and non-disabled based on the modified Rankin scale; those who score 0-2 are defined as non-disabled and those who score 3-5 are disabled. The cost data used in the model for disabled and non-disabled stroke patients were taken from the same source used in the original MTA[3] updated using an inflation index using data from PSSRU.[91] Costs are shown in Table 6-7.

Table 6-7 Stroke event costs

Health state event			Cost*	Reference
Ischaemic stroke	Institutional cost	Non disabled (first cycle)	£5,930	Technology Assessment Report (2004)[3]
		Non disabled (subsequent cycle)	£0	
		Disabled (first cycle)	£12,689	
		Disabled (subsequent cycle)	£0	
		Death	£8,152	
	Non-institutional cost	Non disabled (first cycle)	£413	
		Non disabled (subsequent cycle)	£825	
		Disabled (first cycle)	£1,203	
		Disabled (subsequent cycle)	£2,406	
Haemorrhagic stroke	Institutional cost	Non disabled (first cycle)	£5,930	
		Non disabled (subsequent cycle)	£0	
		Disabled (first cycle)	£12,689	
		Disabled (subsequent cycle)	£0	
		Death	£8,152	
	Non-institutional cost	Non disabled (first cycle)	£413	
		Non disabled (subsequent cycle)	£825	
		Disabled (first cycle)	£1,203	
		Disabled (subsequent cycle)	£2,406	

*uplifted for inflation by a factor of 1.2022 (2003 to 2008)

(ii) Follow-up costs

National Reference costs[70] (2006-07) were used to calculate the hospitalisation costs following CHF and OHEs. The costs used in the model are summarized in Table 6-8.

Table 6-8 Follow up costs

Adverse Event		Cost	Source
Institutional cost	CHF	£878	Technology Assessment Report (2004)[3]
	GI event	£1,211	
	Haematemesis event	£1,211	
	Haematuria event	£807	
	Intraocular event	£1,203	
	Epistaxis event	£0	
	Other event	£1,211	

CHF=congestive heart failure; GI=gastrointestinal

(iii) Drug costs

Costs of drugs include branded cost for MRD+ASA and clopidogrel and generic costs of ASA. The branded drug costs were taken from MIMS[92] (June 2009) and generic ASA cost from BNF 57[93] (March 2009). These costs are shown in Table 6-9.

Table 6-9 Costs of drugs

Drug	Cost	Source
Asasantin (MRD+ASA)	Cost per day= £0.13	MIMS June 2009[92]
Plavix (CLOP)	Cost per day= £1.21	MIMS June 2009[92]
Aspirin (ASA)	Cost per day= £0.02	BNF 2009 Number 57[93]

BNF=British National Formulary; MRD=modified-release dipyridamole; ASA=aspirin; CLOP= clopidogrel; MIMS= monthly index of medical specialties

(iv) Utilities

The utility data for the health states of 'no recurrent IS', 'recurrent IS' and 'haemorrhagic stroke' are taken directly from the PRoFESS[56] clinical trial which used the EQ-5D as a measure at one year and four years. The one year data set was used since it contained the largest number of patients (Table 6-10).

Table 6-10 Utility values at one year in PROFESS study

State	Utility value	Reference in submission	Justification
No recurrent stroke [redacted]	[redacted]	PRoFESS trial data [56, 94]	PRoFESS[56] is the only head-to-head trial of MRD+ASA vs CLOP. It is a large multicentre trial with over 20,000 patients
Recurrent IS [redacted]	[redacted]		
Haemorrhagic stroke [redacted]	[redacted]		

ASA= aspirin; IS= ischaemic stroke; MRD= modified-release dipyridamole.

The manufacturer has used a paper by Miller et al[95] as the source for the disutility value associated with CHF using the mean that is calculated when moving from NYHA II to NYHA III/IV and NYHA I to II (Table 6-11). The disutility value associated with OHE was calculated using utility data presented in Robinson et al[96] and in Brown et al[97] (Table 6-11).

Table 6-11 Disutility associated with CHF and other haemorrhagic events

State	Disutility value	% of haemorrhagic events	Reference in submission	Justification
CHF	0.09 (experienced over 70 days*)	NA	Miller et al[95]	This was based on an 18 month clinical trial (Galbreath et al[98] 2004; Smith et al[99] 2005)
OHE (GI event)	0.16 (experienced over 30 days*)	[redacted]	Robinson et al[96]	This is a standard gamble study (n=180) with an English sample of patients over 60 years old
OHE (Haematemesis event)	0.16 (experienced over 30 days*)	[redacted]	Robinson et al[96]	This is a standard gamble study (n=180) with an English sample of patients over 60 years old
OHE (Haematuria event)	0.16 (experienced over 30 days*)	[redacted]	Robinson et al[96]	This is a standard gamble study (n=180) with an English sample of patients over 60 years old
OHE (Intraocular event)	0.28 (experienced over 30 days*)	[redacted]	Brown et al[97]	Study of 80 US patients, valuing the utility values of macular degeneration.
OHE (Epistaxis event)	0.16 (experienced over 30 days*)	[redacted]	Robinson et al[96]	This is a standard gamble study (n=180) with an English sample of patients over 60 years old
Other event	0.16 (experienced over 30 days*)	[redacted]	Robinson et al[96]	This is a standard gamble study (n=180) with an English sample of patients over 60 years old

CHF=congestive heart failure; GI=gastrointestinal; NA= not applicable; OHE= other haemorrhagic events
* Ten times the mean length of stay in hospital of these patients reported in Department of Health reference cost data. Commercial In-Confidence Information highlighted in blue, underlined and in bold

Summary of submitted results

The base case analysis includes second-line treatment with ASA for those patients discontinuing first-line treatment in clopidogrel and MRD+ASA groups. A summary of the results is shown in Table 6-12 for IS patients and in Table 6-13 for TIA patients.

Table 6-12 Results base case analysis for 1000 IS patients

	MRD+ASA – long term (first-line); ASA (second-line)	**CLOP – long term (first-line); ASA (second-line)**	**ASA**	**No treatment**
Total costs	£37,430,180	£39,238,555	£36,725,769	£36,678,013
Total QALYs	8,724	8,739	8,593	8,596
ICER (MRD+ASA vs...)	-	£114,628	£5,377	£5,910

ASA=aspirin; ICER=incremental cost-effectiveness ratio; MRD=modified-release dipyridamole; QALY=quality adjusted life year; CLOP= clopidogrel

Table 6-13 Results base case analysis for 1000 TIA patients

	MRD+ASA and ASA – long term (first-line); ASA (second line)	**CLOP – long term (first-line); ASA (second-line)**	**ASA**	**No treatment**
Total costs	£37,010,692	£38,871,872	£36,278,556	£36,197,693
Total QALYs	8,781	8,790	8,660	8,675
ICER (MRD+ASA vs...)	-	£199,149	£6,053	£7,684

ASA=aspirin; ICER=incremental cost-effectiveness ratio; MRD=modified-release dipyridamole; QALY=quality adjusted life year; CLOP= clopidogrel

Summary of sensitivity analysis

(i) Deterministic sensitivity analysis

In the scenario SA, statistically significantly different variables were set as central estimates from the PROFESS[56] trial for MRD+ASA and clopidogrel arms i.e. haemorrhagic stroke rates, drop-out rates, OHE and CHF rates; all other transition probabilities were unchanged. Results are shown in Table 6-14 for IS patients and in Table 6-15 for TIA patients. For the reference case (IS patients) one way SA results are also shown in Table 6-16.

Table 6-14 Scenario analysis in 1000 IS patients

	MRD+ASA – long term (first-line); ASA (second-line)	**CLOP – long term (first-line); ASA (second-line)**
Total costs	£37,430,180	£39,897,888
Total QALYs	8,724	8,760
ICER	-	£68,848

ASA= aspirin; MRD= modified-release dipyridamole; CLOP= clopidogrel; QALYs= quality adjusted life years; ICER= incremental cost-effectiveness ratios; IS = ischaemic stroke

Table 6-15 Scenario analysis in 1000 TIA patients

	MRD+ASA – long term (first-line); ASA (second-line)	**CLOP – long term (first-line); ASA (second-line)**
Total costs	£37,195,638	£39,634,600
Total QALYs	8,760	8,799
ICER	-	£62,702

ASA= aspirin; MRD= modified-release dipyridamole; CLOP= clopidogrel; QALYs= quality adjusted life years; ICER= incremental cost-effectiveness ratios; TIA= transient ischaemic stroke

Table 6-16 Results of one way SA of reference case - PRoFESS trial central estimates used for clopidogrel and MRD+ASA (IS patients)

Profile Letter	Sensitivity analysis	Source of sensitivity analysis assumption	ICER (£)
	Base case		£114,628
A	Recurrent IS rate of MRD+ASA used for CLOP		MRD+ASA dominates
B	Haemorrhagic stroke rate of MRD+ASA used for CLOP		MRD+ASA dominates
C	Haemorrhagic stroke rate of MRD+ASA multiplied by factor of 1.12	Estimated 80th percentile using SD data from PRoFESS[56] for IH	£83,105
D	Non-vascular death rate of MRD+ASA used for CLOP		£34,988
E	Vascular death rate of MRD+ASA used for CLOP		£54,949
F	Drop-out rate of MRD+ASA used for CLOP		£234,647
G	Drop-out rate of MRD+ASA multiplied by a factor of 1.1	Assumption in the absence of variance data for a categorical variable from PRoFESS[56]	£88,872
H	OHE rate of MRD+ASA used for CLOP		£122,270
I	CHF rate of MRD+ASA used for CLOP		£113,810
J	Non-drug costs increased by 50%	Assumption	£88,278
K	Utility of haemorrhagic strokes multiplied by a factor of 0.9	Estimated 80th percentile using SD data from PROFESS[56] for IH	£81,498
L	ESPRIT data alone used to estimate ASA vs MRD+ASA (RR)		£95,470
M	ESPS-2 data alone used to estimate ASA vs MRD+ASA (RR)		£183,875

ASA=aspirin; MRD=modified-release dipyridamole; IS=ischaemic stroke; MI=myocardial infarction; RR=relative risk; IH= intracranial haemorrhage; SD=standard deviation; RR= risk reduction; CHF= congestive heart failure; OHE= other haemorrhagic event; ICER= incremental cost-effectiveness ratio; CLOP= clopidogrel

For the scenario sensitivity analysis (IS patients) outlined above, a one-way and two-way SA was also performed Table 6-17.

Table 6-17 One way and two way sensitivity analysis of scenario sensitivity analysis case (IS patients)

Profile Letter (See Table 8 in MS)	Sensitivity analysis	ICER (£)
Base case		£68,848
C	Haemorrhagic stroke rate of MRD+ASA multiplied by factor of 1.12	£58,696
G	Dropout rate of MRD+ASA multiplied by a factor of 1.1	£61,142
J	Non drug costs increased by 50%	£65,838
K	Utility of haemorrhagic strokes multiplied by a factor of 0.9	£60,397
M	ESPS-2 data alone used to estimate ASA versus MRD+ASA RR	£82,148
CG		£53,242
C J		£55,561
CK		£50,922
CM		£68,147
GJ		£58,255
GK		£54,636
GM		£70,110
JK		£57,756
JM		£78,198
KM		£70,690

ASA=aspirin; MRD=modified-release dipyridamole; ICER=incremental cost-effectiveness ratio; IS=ischaemic stroke; MI=myocardial infarction; MRD=modified-release dipyridamole; RR=relative risk;

A SA was performed to demonstrate the impact on the size of the ICER (MRD+ASA vs ASA) of changing the source (ESPRIT[55] or ESPS-2[29]) of the ASA RR data. Using ESPS-2[29] data, the ICER changes from £5,377 per QALY in the base case to £9,535 per QALY for IS patients, and using ESPRIT[55] data changes the ICER from £6,053 per QALY in the base case to £3,948 per QALY for TIA patients.

Probabilistic sensitivity analysis

After generating 500 iterations, the results for the PSA were as follows:

- IS patients: MRD+ASA vs clopidogrel: MRD+ASA has more than 90% probability of being cost effective at a threshold of £30,000 per QALY

- TIA patients: MRD+ASA vs clopidogrel: MRD+ASA has more than 90% probability of being cost effective at a threshold of £30,000 per QALY

Critique of Boehringer-Ingelheim's economic model by the AG

The submitted model considers a wide range of treatment alternatives and describes a wide range of resources to populate the model. The model is mainly based on the PRoFESS[56] trial although some data have been taken from ESPS-2[29] and ESPRIT[55] to obtain probability transitions in the IS group. The transition probabilities during the first four years for the MRD+ASA and clopidogrel arms are derived from the above mentioned trials and beyond that point they have used the same transition probability as used for the last six monthly cycle. This is an unreliable basis for long-term projection since close to the end of the trial patient numbers and the number of events are much reduced. As a consequence estimated incidence rates are very volatile and should not be relied on to drive the major part of the model calculations.

Death rates amongst patients who have had strokes have been derived from two main papers (Bruins Slot et al[90] and Burn et al[89]); when these papers were checked, the figures quoted in Appendix 9 of the MS do not clearly match with those in the published papers. In relation to the TIA incidence rates, the manufacturer has assumed that patients who experienced TIAs had a rate of IS events equal to 80% of those who had experienced a previous IS, there is no evidence to support this assumption and it has not been tested in the one-way SA.

The design of the model also includes tunnel health states to model AEs. The tunnel health states are not depicted in the MS and are poorly addressed in the Excel model. The MS is sometimes hard to follow due to several mistakes in the Appendices notation (e.g. MS, pg27, section 3.2.1) and within the Excel model (e.g. Overview spreadsheet E35 cell in the Excel model says 10 years time horizon instead of 50 years). The figure describing the model (page 25, MS) has two arrows from 'no recurrent stroke' health state to 'non vascular death', which is not consistent with the structure described.

The parameter distributions of costs used in the PSA are not commonly used distributions and their use is not justified by the manufacturer.

The manufacturer states that "MRD+ASA long term first line is cost effective against clopidogrel... Based on these ICERs at a threshold of £20,000 per QALY, it remains cost effective until clopidogrel drops by 45% of brand price for ischaemic stroke patients or 51% for TIA patients" (MS, pg41-42). The AG notes that the generic price of clopidogrel as listed in the Drug Tariff[32] March 2010 is £10.90 (30 X 75mg tablets); this constitutes a 69% reduction in price (branded plavix [£36.35] was used in the model) and means that compared with MRD+ASA, clopidogrel is cheaper and more effective for both IS and TIA populations.

6.2.2 Review of the Sanofi-aventis/Bristol-Myers Squibb submission

Table 6-18 NICE reference case checklist

NICE reference case requirements	Reference case	Does the *de novo* economic evaluation match the reference case?
Defining the decision problem	The scope developed by the Institute	As per the final scope issued by NICE
Comparators	Therapies routinely used in the NHS, including technologies currently regarded as best practice	ASA, CLOP, MRD+ASA, MRD
Perspective on costs	NHS and PSS	As per the final scope issued by NICE
Perspective on outcomes	All health effects on individuals	As per the final scope issued by NICE
Type of economic evaluation	Cost-effectiveness analysis	Cost-effectiveness analysis
Synthesis of evidence on outcomes	Based on a systematic review	All data are derived from head to head trials (mainly CAPRIE[25])
Measure of health benefits	QALYs	QALYs
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	Utilities (MI, PAD, stroke) derived from published, population based studies (TTO or SG); utilities (MVD) based on assumption
Source of preference data for valuation of changes in HRQoL	Representative sample of general public	Population based studies
Discount rate	An annual rate of 3.5% on both costs and QALYs	3.5% per annum for costs and health effects
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	All QALYs estimated by the model have the same weight

ASA=aspirin; LY=life years; QALY=quality adjusted life years; CLOP=clopidogrel; MRD= modified-release dipyridamole; NICE= national institute for clinical excellence' HRQoL= health related quality of life; PSS= personal social services; TTO= time trade off; SG= standard gamble

Overview of submitted manufacturer's submission

A Markov model is designed to assess the cost effectiveness of clopidogrel, MRD+ASA, ASA and MRD alone for the secondary prevention of OVEs: MI, IS, and vascular death. Cost-effectiveness estimates are calculated for four different patient populations:

- patients who have previously suffered an MI
- patients who have previously suffered an IS
- patients who were diagnosed with PAD
- patients with MVD which is described as ischaemic disease in more than one vascular bed.

The same model structure is used throughout, but the baseline risks of vascular events differ for each population. The four treatments under consideration are only compared against each

other in the IS population; while in MI, PAD and MVD populations only clopidogrel is compared with ASA.

The model estimates costs from the perspective of the UK NHS, and health outcomes in terms of life years and QALYs. A cohort of 1,000 patients with the qualifying diagnosis (MI, stroke PAD or MVD) and aged 65 years progresses through the model over a time horizon of 35 years. The starting age of 65 was chosen as the average age in the PRoFESS[56] trial was 66.1, in CAPRIE[25] 62.5 and in REACH[15] 68.6. The cycle length is three months, and only one event can occur in each cycle. The model structure is depicted in Figure 6-2. Costs and benefits have been discounted at a rate of 3.5% per annum.

The model employs six health states (Figure 6-2):

- Initial state: this is the starting condition for all patients, and is considered to be a 'stable' state
- Death: separately recorded for deaths of non-vascular and vascular origin
- History of MI: the condition of patients following a non-fatal MI
- History of stroke: the condition of patients following a non-fatal IS
- History of MI and stroke: the condition of patients who have suffered both a non-fatal MI and a non-fatal stroke
- TA80 state: this intermediate state relates to the TA80 guidance[44] which recommends that treatment with clopidogrel+ASA should be continued for up to twelve months (four cycles in the model) after the most recent acute episode of NSTEMI. In the model, after four cycles, patients go back to antiplatelet monotherapy.

All AEs are included in the cost and QALY calculations, but are not recorded separately as distinct health states or events in the model.

Each patient population (MI, stroke, PAD and MVD) progresses through the model subject to its specific risk profile and parameters depending on previous history. The presence of previous vascular events thus influences the risk of future health states. Patients in the model can either remain stable, experience a MI or a stroke or death (from vascular or non-vascular causes). Deaths within 30 days of a new MI or stroke are defined as vascular deaths, and such patients will progress directly to death.

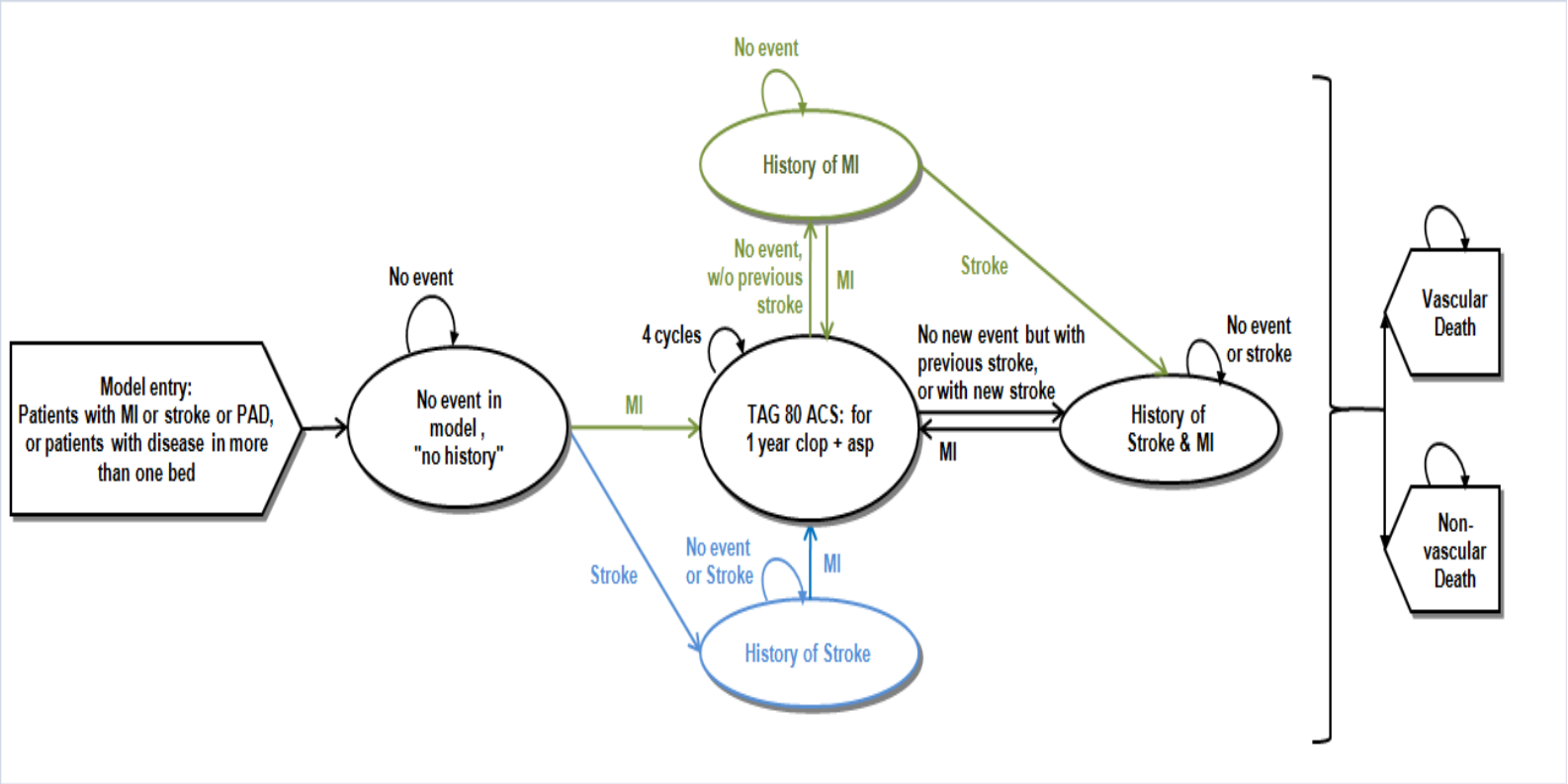

Figure 6-2 Diagram of the Markov model

Summary of effectiveness data

The baseline risk of events related to ASA has been taken from the REACH[15] registry and from a network meta-analysis (NMA) of six studies: ESPS-2;[29] ESPRIT;[55] CAPRIE;[25] MATCH;[57] CHARISMA;[58] and PRoFESS.[56] The REACH[15] registry recruited a large international cohort of patients (N= 68,236) with either established atherosclerotic arterial disease or at least three risk factors for atherothrombosis, and considered the outcomes of CV death, non-fatal MI and non-fatal stroke. The event rates were different for year one (REACH registry[15]), year two (unpublished-academic in confidence) and year three (published on-line[100]). The model assumes the 3-year data to be applicable for all subsequent years (year 3-35).

The manufacturer has constructed a matrix to allocate the correct risk of events to patients as they change health states through the model, such that state and population specific event rates and probabilities are assigned. This trace matrix is reproduced in Table 6-19.

Table 6-19 Trace matrix

Population number after new event			**Health state**			
			No history	**History of NF stroke**	**History of NF MI**	**History of stroke and MI**
Population number at start of model	**1**	**Patients with previous stroke**	1	1	4	4
	2	**Patients with previous MI**	2	4	2	4
	3	**Patients with previous PAD**	3	4	4	4
	4	**MVD patients**	4	4	4	4

NF=non-fatal; MI=myocardial infarction; MVD=multivascular disease; PAD= peripheral arterial disease. Source: Manufacturer submission[51]

The REACH[15] event risks are assumed to be applicable to a population treated with ASA, since 67% of registry patients received ASA monotherapy. Aspirin was chosen to be the treatment of reference to which the three other comparators are modelled. The relative treatment effects of the other three treatments (MRD, MRD+ASA and clopidogrel) vs ASA have been estimated based on direct estimates from clinical trials or indirect estimates from the NMA of the six studies mentioned above. The NMA was conducted for the end-points: stroke; MI; vascular death; non-vascular death; and major and minor bleeding events.

The base case in the model considers all ASA arms in the NMA studies to have equal efficacy. Non-vascular death rates have been derived from life tables. The non-vascular mortality rate is estimated by removing deaths due to the diseases of circulatory system from age-specific deaths from all causes.

The following assumptions were used by the manufacturer in the model:

- Non-vascular death was assumed to be the difference between 'all-cause mortality' and 'death from vascular causes'
- When fatal and non-fatal vascular events were not reported separately, then the total of fatal and non-fatal events was used as an approximation for non-fatal events in the dataset
- In the absence of any evidence on non-vascular death having a dose-response relationship with ASA (in contrast to the vascular events and AEs), it was assumed that the risk of non-vascular death was equal for all ASA doses
- As the ESPRIT[55] trial did not impose a specific ASA dose, but left the decision on dosing to the local investigators, the ASA arm of this trial was assumed to be a weighted average of the low, medium and high ASA dose arms, with weights equal to the proportion of patients observed on the different doses: 46%, 48% and 5%, respectively
- The ATTC data[65] (Antithrombotic Trialists' Collaboration) describing the efficacy of ASA versus no treatment reported only on the composite end-point of 'serious vascular events' but not on the separate components. Therefore the assumption was made that the relative efficacy of ASA versus no treatment was equal for all these separate end-points: MI, stroke and vascular death.

The model presents six different effectiveness analyses derived from the above sources:

1. NMA with the six studies above and ASA doses pooled (base case)
2. NMA splitting up the ASA comparator into three separate comparators: low, medium and high dose ASA
3. Head-to-head analysis based solely on the PRoFESS[56] trial
4. Head-to-head analysis based solely on the CAPRIE[25] trial
5. Head-to-head analysis based on post-hoc analysis on MVD patients from CAPRIE[25] trial.

To estimate the efficacy of clopidogrel+ASA in the TA80[44] state versus ASA, data from the CURE[26] trial have been employed.

Summary of adverse events data

Baseline risk of AEs relating to ASA has been derived from three papers - one meta-analysis[65] and two RCTs.[25, 29] The risk of a major bleeding event is taken from a meta-analysis of RCTs of antiplatelet therapy.[65] The risk of minor bleeding event is derived from the ESPRIT[55] trial. The risk of dyspepsia is taken from the ESPS-2[29] trial comparing ASA to MRD and a combination of MRD+ASA for the secondary prevention of stroke.

Summary of costs and resource use

(i) Event costs

The cost of a non-fatal stroke is a weighted average of the three month cost of an acute mild stroke, a moderate stroke and a severe stroke as estimated from a burden-of-illness model using patient level data.[101]

The cost of a non-fatal MI is taken from a regression analysis[102] calculating the impact of diabetes-related complications on health care costs. This paper also estimates the cost of a vascular death as the average of the cost of a fatal MI and a fatal stroke.

The cost of a non-vascular death is based on an assumption from another economic model[103] which estimated the cost of dying from unrelated causes to be approximately £250.

The cost of a major bleeding event is an average of all Health Related Groups (HRG) Reference Costs[70] that relate to major bleeding reported in the NICE CG36[104] costing report 2006 for atrial fibrillation which mentions calculations for major and minor bleeding events applicable to atrial fibrillation patients.

The cost of a minor bleeding event is mentioned in the NICE report[23] as equal to the cost of a visit to an Accident and Emergency Department, and reported upper and lower limits of £61 and £111.

The AE cost of dyspepsia is taken from a detailed cost analysis[105] of the supply and management of upper GI and renal toxicity related to low-dose ASA use.

All events costs are summarized in Table 6-20.

Table 6-20 Event costs

Event	Cost	Source
Non-fatal stroke	£6,307	Assumption: these costs are estimated from a range of UK specific burden-of-illness papers, where necessary costs have been inflated to represent 2007/08 prices
Non-fatal MI	£4,893	
Vascular death	£2,726	
Non-vascular death	£250	
Major bleed	£2,805	
Minor bleed	£90	
Dyspepsia	£141	
3 months post -stroke	£516	
3 months post- MI	£139	

MI=myocardial infarction

(ii) Follow-up costs

The cost of care three months post-stroke is estimated using the same weighted severity formula[106] used to calculate the costs of non-fatal stroke, and corrects the cost of ongoing care at home and the cost of ongoing care in an institution for the proportion of mild, moderate and severe stroke patients who are discharged to a home or an institution.

The post-MI cost is taken from a regression analysis[102] of costs for a cohort of diabetic patients.

(iii) Drug costs

All annual cost of the treatment are derived from MIMS[92] and are listed in Table 6-21.

Table 6-21 Drug costs

Treatment	Cost per year
ASA (75 mg/day)	£3.50
CLOP (75 mg/day)	£442.26
MRD (2x200mg/day)	£91.25
MRD+ASA (MRD 2x200mg/day + ASA 2x25mg/day)	£94.78

CLOP= clopidogrel; ASA= aspirin; MRD= modified-release dipyridamole
Source: Manufacturer submission[50]

(iv) Utilities

The utility values for patients with a history of stroke, MI or PAD were estimated from a previously published cost-effectiveness analysis,[75] and were derived from published, population-based studies employing either time trade-off or standard gamble techniques. Table 6-22 provides the utility values used in the model. For the stroke utilities, severity specific values were given (mild, moderate and severe), and as for costs, these were weighted to reflect the burden of severity in a patient cohort before being aggregated. The utility value for a patient with MVD is not known, so it is assumed to be the minimum of the three other patient population values, which is the utility value for stroke patients (0.61).

Table 6-22 Utility values

	Patients with previous stroke	Patients with previous MI	Patients with previous PAD	MVD patients
Long term utility values				
No event	0.61	0.87	0.80	0.61
After stroke	0.61	0.61	0.61	0.61
After MI	0.61	0.87	0.61	0.61
After stroke and MI	0.61	0.61	0.61	0.61
Short term decrements after event				
Stroke	-0.174	-0.248	-0.228	-0.174
MI	-0.058	-0.082	-0.076	-0.058
Major bleed	-0.3	-0.3	-0.3	-0.3
Minor bleed	-0.001	-0.001	-0.001	-0.001
Dyspepsia	-0.184	-0.184	-0.184	-0.184

MI=myocardial infarction; MVD=multivascular disease; PAD=peripheral arterial disease Source: Manufacturer submission[50]

In deriving these utility values, the manufacturer has made several assumptions:

- Utilities need to be differentiated based on the baseline health state of the patient; acknowledging the fact that stroke patients and PAD patients might be more disabled and have lower QoL than MI patients
- The utility value for MVD patients should not be higher than the utility for those patients with disease in one vascular bed
- Experiencing a vascular event should decrease QoL temporarily to account for the unpleasantness of the event itself, the time in hospital, recovery time and stress
- After experiencing an event patients should not be better off in the long-term than before the event (i.e. patients experiencing an MI after stroke could not have their utility increased)
- Experiencing AEs (major and minor bleeds) and side effects (dyspepsia) also decreases a patient's QoL in the short term.

The long term utility values for each health state reflect the event history of the patient, that is a patient with MI who then experiences a stroke, is assigned the long term utility value of a stroke, while a patient with MI who experiences another MI is assigned the long term utility value of an MI (so does not suffer any long term decrement). A PAD sufferer, who then experiences an MI, is assigned the long term utility value of a MVD patient.

Summary of results

(i) Stroke patients

The results of the cost-effectiveness analysis for patients who have a history of stroke show that MRD+ASA (or MRD alone) is the most cost-effective treatment. The manufacturer states that if the NHS is willing to pay £31,200 then clopidogrel could be considered as a second line treatment followed by ASA. This appears to be consistent with the efficacy results of the main RCTs, where clopidogrel was shown to be superior to ASA in the CAPRIE[25] trial, and similar to MRD+ASA in the PRoFESS[56] trial (Table 6-23).

Table 6-23 Results for patients with a history of stroke

	ASA	CLOP	MRD+ASA	MRD
Total costs	£10,841	£13,165	£10,948	£10,531
Total QALYs	4.83	4.90	5.28	4.45
Total LYs	7.60	7.75	7.96	6.78
INB vs ASA		-£90	£13,533	-£10,964
INB vs CLOP			-£13,623	£10,875
ICER vs ASA		£31,204	£237	£825
ICER of CLOP vs comparator			CLOP is dominated	£5,850

ICER=incremental cost-effectiveness ratio; INB=incremental net; LYs= life years; benefits; QALYs=quality adjusted life years; Source: Manufacturer submission[50]

(ii) MI patients

Clopidogrel when compared to ASA in the cost-effectiveness model was found to be more effective and more expensive. With an ICER of approximately £21,000 per QALY gained, clopidogrel appears to be a cost-effective treatment for patients with previous history of MI when compared to ASA (Table 6-24).

Table 6-24 Results for patients with a history of MI

	ASA	CLOP
Total costs	£6,349	£8,992
Total QALYs	6.70	6.83
Total LYs	7.55	7.70
INB		£1,194
ICER		£20,662

ICER=incremental cost-effectiveness ratio; INB=incremental net benefits; LYs=life years; QALYs=quality adjusted life years; ASA= aspirin; CLOP= clopidogrel Source: Manufacturer submission[50]

(iii) PAD patients

Clopidogrel was found to be more expensive and more effective than ASA, with an estimated corresponding ICER of £18,854 (Table 6-25).

Table 6-25 Results for patients with a history of peripheral arterial disease

	ASA	CLOP
Total costs	£6,138	£8,608
Total QALYs	5.71	5.84
Total LYS	7.06	7.22
INB		£1,461
ICER		£18,854

ICER=incremental cost-effectiveness ratio; INB=incremental net benefits; LYs=life years; QALYs=quality adjusted life years; Source: Manufacturer submission[50]

(iv) Multivascular disease patients

In this population it was found that clopidogrel was cost effective compared with ASA with an estimated ICER of £15,524 per QALY gained (Table 6-26).

Table 6-26 Results for patients with a history of multivascular disease

	ASA	CLOP
Total costs	£8,678	£10,483
Total QALYs	4.68	4.80
Total Lys	6.00	6.13
INB		£1,683
ICER		£15,524

ICER=incremental cost-effectiveness ratio; INB=incremental net benefits; LYs=life years; QALYs=quality adjusted life years; Source: Manufacturer submission[50]

Summary of sensitivity analysis

The manufacturer has reported a deterministic scenario analysis using the different efficacy analyses included in the model. In the stroke population, clopidogrel is dominated by MRD+ASA in all the possible efficacy analyses, and with or without treatment effect for non-vascular death. Clopidogrel is shown to be cost effective when compared with ASA using CAPRIE[25] data only in both treatment effect scenarios for non-vascular death (Table 6-27).

Table 6-27 Summary of ICER for patients with a history of stroke with and without treatment effect for non-vascular death

Assumption: treatment effect for non-vascular death	With assumption	Without assumption
	ICER CLOP vs ASA	ICER CLOP vs ASA
NMA of ASA doses pooled (base case)	£31,204	£27,749
NMA of low, medium and high dose ASA	£58,070	£46,500
CAPRIE[25] data only	£28,486	£24,010

NMA=network meta-analysis; ASA= aspirin; CLOP= clopidogrel; ICER= incremental cost-effectiveness ratio

The ICERs for the other populations (MI, PAD and MVD) also change slightly with the assumption concerning the treatment effect for non-vascular death in each of the efficacy analyses, resulting in clopidogrel appearing cost effective with an ICER below £30,000 per QALY. The best results for clopidogrel are in MVD patients using data from the post-hoc CAPRIE[25] trial efficacy analysis.

In summary, the cost effectiveness of treatments for the secondary prevention of OVEs is sensitive to a range of different scenarios. Removing the treatment effect on non-vascular deaths is found to improve the cost-effectiveness estimates of clopidogrel. Cost effectiveness is also found to be sensitive to the efficacy estimates: taking account of different ASA doses worsens the cost-effectiveness estimates, while using only a head-to-head analysis based on the CAPRIE[25] trial improves them. The estimates in the stroke population are least sensitive to a head-to-head analysis using the PRoFESS[56] trial.

A PSA was developed by the manufacturer using a Monte Carlo simulation undertaking 3,000 iterations. At a threshold of £30,000 per QALY, the treatment option with the highest probability of being cost effective in MI, in PAD and MVD populations is clopidogrel; and in stroke it is MRD+ASA as Table 6-28 shows.

Table 6-28 Probability of being cost effective for each patient population

Treatment	Threshold/QALY	Population			
		Stroke	MI	PAD	MVD
ASA	£20,000	0%	51%	48%	41%
CLOP	£20,000	0%	49%	52%	59%
MRD+ASA	£20,000	97%			
MRD	£20,000	3%			
ASA	£30,000	0%	40%	36%	32%
CLOP	£30,000	0%	60%	64%	68%
MRD+ASA	£30,000	97%			
MRD	£30,000	3%			

ASA=aspirin; CLOP= clopidogrel; MRD=modified-release dipyridamole; Source: Manufacturer submission[50]

In stroke patients, the average incremental net benefit (INB) of clopidogrel when compared with ASA is -£6 with an associated 95% CI of -£6,320 to £7,279.

The PSA in MI patients reports an INB of £1,187 (CI -£7,692 to £10,260). The cost-effectiveness acceptability curve (CEAC) shows that for a threshold of £30,000 per QALY clopidogrel is cost effective in 60% of the iterations.

For patients with PAD, the PSA estimates an average INB of clopidogrel vs ASA of £1,475 (CI -£6,106 to £9,476). The CEAC suggests that there is a 64% probability that, at a threshold of £30,000 per QALY, clopidogrel would be considered a cost-effective treatment for the prevention of OVEs.

For patients with MVD, the average INB of clopidogrel versus ASA is £1,748 (CI -£5,475 to £9,179) and the CEAC suggests there is a 68% probability of clopidogrel being cost effective at a threshold of £30,000 per QALY.

Critique of Sanofi-aventis and Bristol-Myers Squibb's economic model

The manufacturer of clopidogrel has presented "new" evidence of the clinical and cost effectiveness of clopidogrel on a set of four re-allocated patient populations (stroke, MI, PAD and MVD) this means that none of the effectiveness results used in their modelling of cost effectiveness are directly derived from publications from the CAPRIE[25] trial. The review group accepts that this new categorisation is more appropriate and results in better defined and less heterogeneous patient groups. However, the details that would be required to construct and populate a long-term disease model based on CAPRIE[25] are not available beyond the summary statistics presented in the manufacturer's submission.

The AG notes that the generic price of clopidogrel as listed in the Drug Tariff[32] March 2010 is £10.90 (30 X 75mg tablets); this constitutes a 69% reduction in price (branded plavix [£36.35] was used in the model). Using this new price in the model improves the cost effectiveness of clopidogrel.

The manufacturer's model is depicted in Figure 6-2 and includes one health state called 'TA80 ACS' which represents treatment after an MI following the TA80[44] guidelines in the treatment of patients with NSTEMI. This document refers only to NSTEMI patients yet the MS does not differentiate between STEMI and NSTEMI patients so the model does not reflect clearly the recommended treatment of patients following an MI.

The baseline event rates in the ASA arm are taken from the REACH[15] registry whose population is a mixed population of patients with history of MI, stroke, PAD and patients with risk factors of cardiovascular disease. The original scope issued by NICE does not mention risk factors, only history of previous events. Also these baseline event rates have been applied to patients in the ASA group; however, only 67% of the population the REACH[15] registry have received ASA monotherapy.

The model assumes different transition probabilities every year until year three. Beyond this point the last-cycle transition probabilities are used for the remainder of the time horizon from year 3 to 35. This is an unreliable basis for long-term projection since close to the end of the trial patient numbers and the number of events are much reduced. As a consequence estimated incidence rates are very volatile and should not be relied on to drive the major part of the model calculations.

Calculations used to derive utilities are adequately described in the MS but sometimes differences between AEs utilities are not clearly explained (e.g. decrement utility after major bleed and minor bleed: there is a substantial difference between them which is not discussed). Also utility values are calculated using an assumption of perfect health for patients before the event: 1 ('utility' spreadsheet in the model) and this is inappropriate.

In the model, half-cycle correction and discount rate methodologies have been applied incorrectly; this affects the final results of the model and overestimates the number of QALYs generated.

6.2.3 Summary critique of models submitted by the manufacturers

The economic models submitted by the manufacturers are structured in terms of a limited number of disease states which are presumed to be largely homogeneous with respect to health costs and QoL. Moreover, the models do not allow previous health history to be preserved except in the simplest form. There are real dangers that significant interactions between competing risks (e.g. MI vs stroke, vascular death vs non-vascular death) may not be accurately represented in these Markov formulations, and that initially minor anomalies can be amplified to large errors when extrapolated over a lifetime. The details that would be required to construct and populate a long-term disease model based on CAPRIE[25] and PRoFESS[56] are not available beyond the summary statistics presented in the MS. Moreover, the revised definitions for assigning patients to the new groups are not completely clear, leading to some concern of how such data should be modelled. To reduce this problem the AG requested that a set of analyses should be carried out by the manufacturer to allow a new model to be developed and calibrated for these four patient groups. For this we provided appropriate definitions of each population, and detailed specifications of the three types of analyses required: survival analyses (Kaplan-Meier and Cox regressions), numbers of outcome events and patient exposure to risk, and event fatality (See Appendix 9 for details).

6.3 Independent economic assessment

6.3.1 Methods

Approach to modelling occlusive vascular events

Modelling disease-related health and the economic effects of chronic lifetime conditions presents additional and different challenges to those encountered when dealing with conditions of an acute or time-limited nature. In particular, over a lifetime, patients are subject to multiple interacting competing risks of fatal and non-fatal events, and the accumulation of complex and dynamic health histories with a resulting dynamic pattern of prognostic risks. To overcome these challenges the AG has chosen to develop a new model of OVEs involving individual patient sampling. Instead of considering patients in aggregated groups with average characteristics, we generate a series of individual patients whose combined characteristics are representative of the specified population. The advantage of this approach is that individual patient histories can be generated according to a number of known competing risks, so that interactions are automatically accounted for.

Obtaining these advantages often involves significant technical costs in terms of complex programming and long processing times which involve the use of very large numbers of random numbers in order to achieve stable results. To reduce these difficulties the AG has designed the model structure to operate within a Microsoft Excel workbook with limited additional coding and incorporating several 'variance reduction' techniques.

Patient populations

Four mutually exclusive patient populations are modelled using the following definitions:

MI only

This population is defined as patients suffering a recent acute MI, who may have a prior history of ischaemic heart disease but have no prior history of IS, TIA or PAD.

Stroke/TIA only

This population is defined as patients suffering a recent IS or TIA, who may have a prior history of ischaemic cerebrovascular events, but have no prior history of ischaemic heart disease (including MI) or PAD.

PAD only

This population is defined as patients suffering a recent episode of PAD, but who have no prior history of IS or TIA, or ischaemic heart disease (including MI).

MVD

This population is defined as patients suffering a recent episode of acute MI, IS or TIA, or PAD, and who have a prior history involving at least one other type of vascular disease.

In order to characterize each of these populations in terms of age and gender, an analysis of data from the Health Survey for England 1996[107] has been carried out, using data on self-reported chronic health conditions to identify samples corresponding to the four modelled populations[a] (Table 6-29).

Table 6-29 Modelled populations: age and gender

	IS only			MI only			PAD only			MVD		
	Age		Propn	Age		Propn	Age		Propn	Age		Propn
	Mean	SD	%	Mean	SD	%	Mean	SD	%	Mean	SD	%
Male	67.75	12.95	54.9	65.01	11.96	49.9	61.75	13.96	48.6	63.92	11.33	53.1
Female	67.62	12.97	45.1	70.50	9.67	50.1	65.17	15.98	51.4	70.39	11.63	46.9

IS=ischaemic stroke; MI=myocardial infarction; MVD=multivascular disease; PAD= peripheral arterial disease; propn=proportion; SD= standard deviation

[a] The Health Survey for England 1996 was commissioned by the Department of Health and carried out by the Joint Surveys Unit of Social and Community Planning Research and the Department of Epidemiology and Public Health at University College London, who bear no responsibility for the analysis or interpretation of its data presented in this report.

Treatment strategies

It is clear from the available evidence[55, 56] that a significant proportion of patients do not persist with the medication initially prescribed, either because of unacceptable AEs of the drug, or for other personal or lifestyle reasons. When discontinuation occurs, it is necessary to prescribe an appropriate alternative treatment if one is available; as a consequence, the effect of treatment on future risks will be modified. It is therefore necessary to assess the effectiveness and cost effectiveness of preventive medicines within the framework of life-time treatment strategies. Table 6-30 and Table 6-31 set out the treatment strategies which may be compared using the economic model for each patient population.

Table 6-30 Treatment strategy: IS/TIA population

Intolerance				Strategy stages		
None	**ASA**	**MRD**	**ASA & MRD**	**Treatment 1**	**Treatment 2**	**Treatment 3**
√	√	√	√	Nothing	Nothing	Nothing
√	x	√	x	ASA	Nothing	Nothing
√	√	√	√	CLOP	Nothing	Nothing
√	x*	x	x	MRD+ASA	Nothing	Nothing
√	x	√	x	ASA	CLOP	Nothing
√	x	x	x	ASA	MRD+ASA	Nothing
√	x	√	x	CLOP	ASA	Nothing
√	x*	x	x	CLOP	MRD+ASA	Nothing
√	x	x	x	MRD+ASA	ASA	Nothing
√	x*	x	x	MRD+ASA	CLOP	Nothing
√	x	x	x	ASA	CLOP	MRD+ASA
√	x	x	x	ASA	MRD+ASA	CLOP
√	x	x	x	CLOP	ASA	MRD+ASA
√	x	x	x	CLOP	MRD+ASA	ASA
√	x	x	x	MRD+ASA	CLOP	ASA
√	x	x	x	MRD+ASA	ASA	CLOP

ASA=aspirin; MRD=modified-release dipyridamole; IS= ischaemic stroke; TIA= transient ischaemic attack; CLOP= clopidogrel
x* = viable if MRD+ASA replaced by MRD

Table 6-31 Treatment strategy: MI only, PAD and MVD populations

Intolerant to ASA	Strategy stages		
	Treatment 1	**Treatment2**	**Treatment 3**
√	Nothing	Nothing	Nothing
x	ASA	Nothing	Nothing
√	CLOP	Nothing	Nothing
x	ASA	CLOP	Nothing
x	CLOP	ASA	Nothing

ASA=aspirin; MRD=modified-release dipyridamole; CLOP= clopidogrel

Model design

The logic flow for generating a full patient history for each sampled patient is shown in Figure 6-3 for the first two key events. Since event times are estimated as continuous variables, it is not possible for a conflict to arise with two events occurring simultaneously. Subsequent events repeat the same pattern. Each patient continues to accumulate additional events until a fatal event is encountered.

Key events

The following are identified as events which determine the event history of each modelled patient:
- a new fatal or non-fatal IS event
- a new fatal or non-fatal non-ischaemic stroke event (haemorrhagic stroke or intra-cranial haemorrhage)
- a new fatal or non-fatal MI
- death from other vascular causes
- death from non-vascular causes
- patient discontinues current preventive medication for any reason.

When any of these events occurs, the age, disability status and event history of the patient is updated to the time of the latest event and the current preventive medication is updated if necessary to the next stage of the defined treatment strategy. The revised patient details are then used to estimate likely event times for the next key patient event until death occurs.

Other events

Additional non-fatal events may also occur to patients and are estimated independently of the main event pathway to ensure their effects on patient experience and healthcare resource use are captured by the model. The current model includes several recognised AEs associated with antiplatelet therapy (major and minor bleeding, gastric problems, etc) and additionally new/worsened CHF as a possible event.

Disability

Continuing functional disability resulting from stroke events is known to be a prognostic indicator for high event risks and greater mortality amongst affected patients.[90] The model includes a binary measure of functional disability equivalent to scores of three or more on the modified Rankin scale.[59] The risk of progression to disabled status following a stroke event was derived from an analysis of PRoFESS results[108] and is used as a risk modifier for subsequent events.

Risk models

Confidential information from the two key clinical trials (CAPRIE[25] and PRoFESS[56]) has been provided to the AG in order to allow calibration of the model, and in particular to facilitate development of risk models incorporating all relevant modifying variables, and avoiding errors arising from incorrect application of competing risks. Full details of the derived parameter values for all model events are provided in Appendix 10.

Event fatality

Data from the CAPRIE[25] trial provided by the manufacturer of clopidogrel has allowed separate fatality risk models to be developed for the three primary vascular events. Details of the analysis and parameter values are shown in Appendix 11.

Duration of treatment

Some patients taking continuous preventive medication will eventually discontinue treatment for a variety of reasons. Analysis of clinical trial data from PRoFESS[56] and ESPRIT.[55] (Appendices 5-7 of Boehringer Ingelheim MS) indicates that continuance falls steadily over time, but that a substantial proportion of patients will continue taking the prescribed treatment indefinitely. The most appropriate representation is found to be an exponential survival function, with a minimum 'floor' probability of continuing treatment. Survival functions have been estimated for clopidogrel from PRoFESS[56] data, for MRD+ASA from PRoFESS[56] and ESPRIT,[55] and for ASA alone from ESPRIT[55] (Table 6-32). A random number is used to place each patient/treatment combination on the appropriate survival curve and to calculate the corresponding time of discontinuation. A facility is included to limit the duration of any treatment to a pre-specified maximum duration after which the patient automatically progresses to the next step in the treatment strategy.

Table 6-32 Parameters for continuation probability models

	Model parameters*		
Treatment	A	B	k
CLOP	[redacted]	[redacted]	[redacted]
MRD+ASA	[redacted]	[redacted]	[redacted]
ASA	[redacted]	[redacted]	[redacted]

CLOP= clopidogrel; MRD= modified-release dipyridamole; ASA= aspirin

*Probability of continuing treatment at time t years = $A \cdot B^{(1 - \exp(-k.[t - 0.5]))}$

MRD assumed to have the same characteristics as MRD+ASA

Resource use

Health care resource use is measured in terms of clinical events and time spent in chronic states, as well as duration of continuing medication as follows:

Events

Ischaemic stroke (fatal/non-fatal)

Non-ischaemic stroke (fatal/non-fatal)

Myocardial infarction (fatal/non-fatal)

Other vascular event (fatal)

Non-vascular death

Adverse events related to medication

Chronic states

Prior disabling stroke

No prior disabling stroke

Prior MI

History of PAD

History of MVD (disabled / non-disabled)

Cost estimates

Unit costs are drawn from a variety of sources, including those used in the two MS.[50, 51] In all cases the latest costs/prices have been used[32, 109, 110] and where appropriate costs have been inflated to 2009 prices using the Hospital and Community Health Services price inflation index reported by the PSSRU.[91]

Key events: Unit costs for the primary events projected in the model are shown in Table 6-33, distinguishing between disabling and non-disabling strokes. The model logic uses two parameters for non-fatal stroke and MI events in which an event cost is assigned to a patient at the time of the event (assumed to encompass excess early recovery/rehabilitation costs not covered by long-term service use) and a continuing care cost related to the time following the time of the event until the patient's status changes.

Costs for stroke events are taken from Youman,[101] uplifted for inflation from 2001. Myocardial infarction costs are more problematic, since the only source cited by either manufacturer (UKPDS 65)[102] relates only to patients with type 2 diabetes who are known to incur substantially greater unit costs for all types of health care (both in terms of frequency and intensity of resource use). The main

trials (PRoFESS[56] and CAPRIE[25]) only include a minority of patients with diabetes, reflective of the prevalence within the general population of vascular patients, and therefore there is a likelihood that without adjustment these costs will be overestimated. In the UKPDS paper[102] two MI costs are estimated: an average for all patients (including 20-26% who received no in-patient care), and a greater average only for those patients admitted to hospital. In recognition of the risk of overestimating MI costs from this source, we selected the lower figure for both fatal and non-fatal MIs and uplifted these unit costs for inflation from 1999.

Table 6-33 Unit costs for key model events by disability status

Key model event	Patient status	
	Not disabled (Rankin 0-2)	Disabled (Rankin 3-5)
Non-fatal ischaemic stroke	£6,409.94	£13,647.38
Fatal ischaemic stroke	£8,767.69	£8,767.69
Non-fatal haemorrhagic stroke / ICH	£6,409.94	£13,647.38
Fatal haemorrhagic stroke / ICH	£8,767.69	£8,767.69
Non-fatal MI	£5,761.88	£5,761.88
Fatal MI	£2,218.39	£2,218.39
Other vascular death	£2,225.00	£2,225.00
Other non-vascular death	£2,225.00	£2,225.00

MI= myocardial infarction; ICH= intracranial haemorrhage

Continuing care: Estimated unit costs are shown in Table 6-34. For stroke survivors, the annual costs of on-going health and social care services are based on the estimates produced by Youman[101] uplifted for inflation from 2001. For non-disabled stroke survivors the non-institutionalised unit cost was used, and for disabled survivors a weighted average of patients living at home and in institutions was calculated. For non-fatal MI patients, continuing care costs were obtained by combining the in-patient and out-patient costs reported in UKPDS65,[102] uplifted for inflation from 1999. Continuing care costs are assumed to be hierarchical on the basis of accumulating patient history; so a patient suffering a stroke will continue to incur the higher care costs even after surviving a subsequent MI.

Table 6-34 Unit costs for key model events by disability status

Patient status	Annual continuing care cost
No key events	£0.00
Non-fatal MI	£577.60
Non-fatal non-disabling stroke	£1,686.04
Non-fatal disabling stroke	£5,175.44

MI= myocardial infarction

Adverse events: To estimate the costs of AEs related to the various treatments we chose to adopt the categories used in the Sanofi-aventis/Bristol-Myers Squibb submission (major/minor bleeding and dyspepsia) but have also incorporated hospital events involving the initiation or worsening of CHF as used in the Boehringer-Ingelheim submission.[50] Table 6-35 shows the frequency parameters used, as well as the unit costs. Costs have broadly followed the methods used by the manufacturers, but using the latest cost sources, and inflating costs to 2009. The overall average annual costs are applied to all patients for the periods when each of the treatments is in use.

Table 6-35 costs for adverse events by type of treatment

		Annual event frequency by treatment*				
Adverse event	**Unit cost**	**ASA**	**CLOP**	**MRD**	**MRD/ASA**	**None**
Major bleeding event	£2,010.35	0.54%	0.41%	0.13%	0.46%	0.00%
Minor bleeding event	£111.57	0.93%	0.93%	0.38%	0.87%	0.00%
Dyspepsia	£146.61	2.33%	1.99%	5.85%	6.19%	0.00%
CHF event/worsening	£1,074.92	0.63%	0.75%	0.63%	0.63%	0.63%
Combined average cost		**£22.08**	**£20.10**	**£18.42**	**£26.18**	**£6.80**

CLOP= clopidogrel; MRD= modified-release dipyridamole; CHF= congestive heart failure; ASA= aspirin
*Frequency values for bleeding events and dyspepsia taken from BMS model. CHF frequency is the overall average value in the PRoFESS trial since there is no evidence of increasing/decreasing time trends.

Antiplatelet therapy: The estimated NHS cost of each component of anti-platelet therapy is shown in Table 6-36, for the relevant periods of treatment. Clopidogrel has recently become available to the NHS at a slightly reduced price, though it should be noted that the generic form is not licensed for all indications covered by the branded product.

Table 6-36 Unit costs for adverse events by type of treatment

Treatment	**Dose**	**Annual cost**	**4 weeks cost**	**Single dose**	**Source**
ASA	75mg daily	£6.9888	£0.5350	-	BNF 58[31]
MRD	200mg twice daily	£91.3125	-	-	BNF 58 /NHSDT (April 2010)[32]
MRD+ASA	200mg/25mg twice daily	£94.8433	-	-	BNF 58[31]
CLOP (branded)	300mg	-	-	£4.8473	BNF 58[31]
CLOP (branded)	75mg daily	£442.5613	£33.9267	-	BNF 58[31]
CLOP (generic)	75mg daily	£132.7075	£10.1733	-	NHSDT (April 2010)[32]

BNF= British National Formulary; NHSDT= NHS Drug Tariff; CLOP= clopidogrel; MRD= modified-release dipyridamole; ASA= aspirin

Health valuation

Health utility values are drawn from a variety of sources, including those used in the two MS.[50, 51] Mean utility values are assigned to each chronic health state, and a specific utility decrement effect is applied for each modelled event.

EuroQol EQ-5D data collected in the PRoFESS[56] trial have been used to estimate the utility for IS patients prior to any subsequent key events ([redacted]), and to determine the long-term utility decrement applicable to suffering stroke-related disability ([redacted]). In addition, the PRoFESS[56] results allowed utility decrements to be applied following the first subsequent non-fatal key event ([redacted]), as well as a single decrement for more than 1 subsequent key event ([redacted])

The utility values used in the Sanofi-aventis/Bristol-Myers Squibb model for MI and PAD without a subsequent key event (0.87 and 0.80 respectively, drawn from a study by Schleinitz[74]) are adopted here. Though no data can be traced relating to MVD patients, we have assumed that they are likely to begin treatment with a rather worse HRQoL than patients with only a single type of vascular disease, and we have adopted a value of 0.75.

The estimate of utility decrement applicable to a CHF event used in the Boehringer-Ingelheim model appears to be well-sourced and has been adopted for this model indicating an event decrement of -0.0163 QALYs. The utility impact of the other events (major/minor bleeding events and dyspepsia) proved more difficult to identify.

The reference given for a minor bleed (Sullivan[111]) draws upon an earlier paper by O'Brien[112] which lists the source as 'assumption'. The suggested decrement (-0.2) is relative to a theoretical 'perfect health' state rather that of a patient with established chronic disease and so may be overstated. Since this condition is only considered to last for two days the magnitude of this factor in determining cost-effectiveness must be very small, and we have adopted a notional decrement of -0.0033 QALYs in the absence of any more reliable source.

The estimate for dyspepsia is drawn directly from Jansen[113] but fails to recognise that each event is estimated to last just three weeks rather than the 13 weeks used in the BMS model. Adjusting for this problem yields an estimated utility decrement per event of -0.0106 QALYs.

The Sanofi-aventis/Bristol-Myers Squibb utility calculations for major bleeding events draw on three patient categories in Jansen's paper[113] for gastro-intestinal events (out-patient treatment, in-patient treatment and treatment involving surgery) and one for ICH events (Quinn[114]). Only one of the figures used from Jansen's paper[113] can be traced and validated from the original sources, and the events are taken by Jansen[113] to last for five weeks, rather than the 13 weeks implicit in the Sanofi-aventis/Bristol-Myers Squibb model. The paper by Quinn[114] uses a crude approach to estimating the utility decrement of an ICH event, involving an assumption that utility falls from 1.0 ('perfect health') to 0.0 ('death') for the whole duration of the event, estimated at 11 weeks. This must be taken as a substantial over-estimate. Reworking these calculations suggests a decrement in utility from a major bleeding event of -0.1426 QALYs (compared to the Sanofi-aventis/Bristol-Myers Squibb estimate of -0.3003 QALYs).

In principle utility decrements should be considered for both long-term state of a patient following a significant event, and also associated with the short-term impact of the event in the immediate acute and post-acute periods. Only one study[115] has been identified which has attempted in any way to discriminate between these two effects; in Table 2 of their paper[115] the authors report results of two regression analyses involving parameters which distinguish the effect of events in the last 12 months from those in previous years. Subtracting the estimated long-term value from the short-term value should indicate[113] the magnitude of the short-term excess disutility associated with experience of the event itself. However, the results are inconclusive, since this approach appears to indicate a net utility gain from a stroke which is not clinically meaningful. Moreover the numbers of recorded events are insufficient to generate statistically significant differences between coefficients. As a result it has been concluded that it is not currently possible to assign meaningful disutility estimates to model events in addition to the long-term state-related impact described above, and this element of utility estimation has been omitted.

Discounting

Discount rates of 3.5% for both costs and health outcomes (life years and QALYs) are used. Discounting is applied annually after the first year.

Time horizon

A lifetime perspective is taken for the model.

Variance reduction

Two specific measures are implemented in the model to limit background random variation and improve efficiency of model performance.

Random assignment of age/sex is not employed for individual patients. Instead, 100 points across the standard normal probability distribution are used to define a distinct set of baseline ages for each sex drawn from the specified population providing a fully representative spread of patients by age and sex. This basic set is then reproduced ten times to yield a total of 2,000 individual patients. Finally results are generated separately for males and females, and overall mixed population results are obtained by applying the appropriate gender proportions to yield weighted averages.

The random numbers which govern the occurrence of events are not generated every time that the model is run. Instead a full set of random numbers is stored and accessed identically for each patient when generating patient histories for different treatment strategies. This ensures that differences apparent in the results obtained are solely due to the difference in treatments and are not arising from the uncontrollable impact of large numbers of 'in-process' random fluctuations. The stability of the incremental results obtained can be assessed by comparing results from a number of stored random number sets.

Assessment of uncertainty

Univariate SA is carried out for a full range of model parameters.

Other modelling issues

Three modelling difficulties are apparent from consideration of previous technology appraisals and the related NICE guidance.

Modelling TIA

The TAR[3, 23] which led to the development of the current guidance on secondary prevention of OVEs included some consideration of patients suffering from TIA despite the absence of separate trial information for the effectiveness of either treatment for this patient group. A simple assumption was made that TIA patients were at risk of future events at a reduced (80%) rate compared to IS patients. This failed to take into account two published papers presenting results from the Oxfordshire Community Stroke Project, showing the risk of stroke following a first-ever stroke,[89] or following a TIA.[116] More recently a Canadian population study[117] provided similar findings for TIA patients. Table 6-37 does not suggest that there is strong evidence to make a distinction between TIA patients and those surviving an IS. On this basis it has been assumed that TIA patients may be subsumed within the stroke model population since long-term risks appear to be similar.

Table 6-37 Future risk of stroke following TIA or stroke in community

Population	Stroke risk at 12 months % (95% CI)	Stroke risk at 5 years % (95% CI)
Oxford stroke patients	13.2% (10.0-16.4)	29.5% (19.8-39.0)
Oxford TIA patients	11.6% (6.9-15.8)	29.3% (21.3-37.3)
Alberta TIA patients	14.5% (12.8-16.2)	-

TIA= transient ischaemic attack; CI= confidence interval

TA80 guidance and the myocardial infarction population

On the basis of evidence from the CURE[26] trial, NICE guidance document TA80[44] recommends that patients surviving a NSTEMI event should receive clopidogrel and low-dose ASA as medication for the prevention of further MI events for a period of 12 months, followed by low-dose ASA alone thereafter. There is no current guidance for surviving STEMI patients beyond the immediate post-MI period.

The only clinical trial evidence submitted for the current appraisal relating to the MI only patient population is from a subgroup of the CAPRIE[25] trial population, which involves a mix of STEMI and NSTEMI patients. No analyses are provided in the CAPRIE[25] clinical study report distinguishing between STEMI and NSTEMI patients.

Similar concerns apply to the MVD population, since a proportion of these patients may have MI as the qualifying event. No information is available on the composition of the MVD group in CAPRIE[25] by qualifying event so it is difficult to determine how any meaningful subdivisions could be applied.

As reviewing the existing TA80 guidance[44] and CG48 guidelines[7] is not within the scope of this appraisal, it is necessary to assume that recommendations for post-MI preventive treatment of both NSTEMI and STEMI patients remain valid. However, it would be inappropriate to begin modelling MI only patients whilst still subject to these short-term provisions (12 months for NSTEMI and four weeks for STEMI patients). We therefore assume that all MI only patients have survived to the end of the specified period without suffering a further MI, or any other OVE (which would require them to be reclassified as MVD patients), prior to embarking on the chosen long-term preventive treatment strategy. This avoids the necessity of identifying MI patients as either STEMI or NSTEMI from the outset.

TA80 and subsequent myocardial infarction events in all populations

In all four populations defined above there is a risk of future MI events, some of which will be non-fatal. Therefore, the TA80 guidance[44] requires that the affected patients (i.e. those suffering an NSTEMI event) should be switched to clopidogrel+ASA for twelve months. For modelling it becomes necessary to estimate the probability of NSTEMI vs STEMI to assign the correct post-event short-term treatment, although none of the available trials provide information on the type of MI

suffered. The GRACE[118] study of ACS patients is used to estimate the proportions of STEMI:NSTEMI in the population as 53.8%:46.2% (MIs excluding unstable angina). To accommodate the effects of TA80 guidance[44] in the model a simplification has been applied, which involves a reduction to the short-term post-MI risk which was estimated from the CAPRIE[25] data to reflect the benefits observed in CURE,[26] and a corresponding short-term increase in treatment costs for the 12 months post-MI, both averaged by the STEMI:NSTEMI proportions in the GRACE[118] study.

In addition, the follow-on treatment after twelve months (ASA alone or 'standard care') needs to be interpreted in the context of the model treatment strategies. Where an 'MI only' patient suffers subsequent MI events, but no other type of occlusive event, treatment may resume at the stage of the treatment strategy prior to the latest MI(s) requiring short-term follow-up. If an 'MI only' patient suffers a different kind of occlusive event, they attract the higher risks associated with MVD patients for the remainder of their life. In the same way a 'stroke only' or 'PAD only' patient suffering an MI will also be subject to the higher MVD risks once the short-term follow-up care is complete. Equally, an 'MI only' or 'PAD only' patient suffering an IS may receive up to two years MRD+ASA treatment as required by TA90,[23] and subsequently resume the long-term care strategy subject to the increased MVD event risks.

TA90 and subsequent ischaemic stroke events in all populations

NICE TA90 guidance[23] recommends the use of MRD+ASA for up to two years following a non-fatal IS event. The AG model has been adapted to reflect this feature, which may be rendered active or inactive at the user's discretion. The adaptation involves introducing a pseudo-event at end of the TA90[23] recommended treatment period, before the patient resumes at their prior stage in the assigned treatment strategy. This is an effective mechanism for coping with the added complexity of TA90 guidance.[23] However, it does result in some potential loss of integrity in the matching of random number sequences between comparator model runs (a mechanism used for 'variance reduction' in the model); in principle this might introduce some element of bias into the results, but it would only occur in the latter stages of a patient's career when many patients have already died, and appears more likely to underestimate incremental differences than to overestimate them. A simple test of this effect is to compare model results with and without this feature activated, since the model results obtained when the TA90[23] feature is inactive are not subject to any potential bias. To date the AG has not detected any evidence of any bias affecting the decision analysis results.

A note of caution is necessary here against attempting to use a comparison of model results with and without the TA90[23] feature turned on as a means of reconsidering the validity of TA90 guidance.[23] As currently constructed the model would not be valid for this purpose, and would require important modifications to achieve such an objective. Since this is not within the scope of the current appraisal no effort has been made to pursue this possibility.

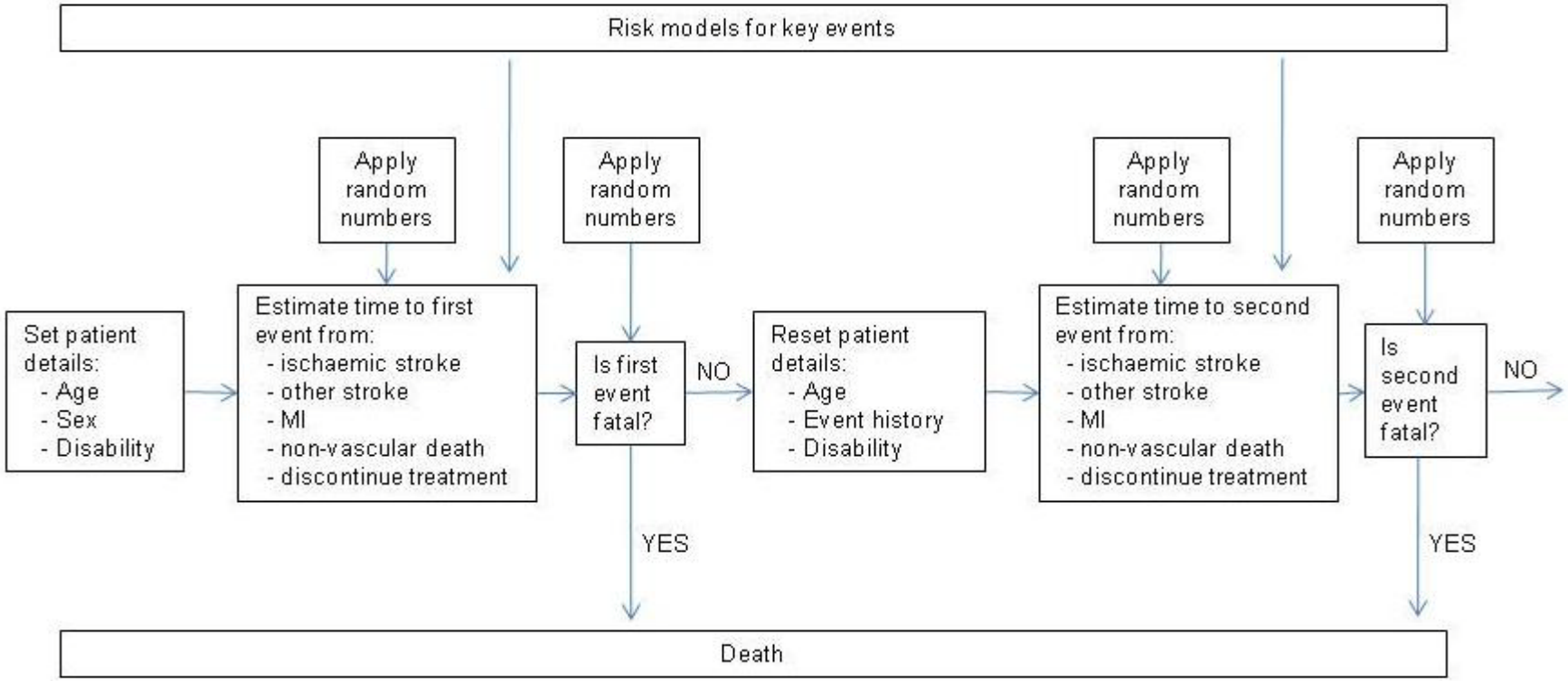

Figure 6-3 Patient sampling model flowchart for a sequence of key events within a single patient history

6.4 Independent economic model results

Results have been generated from the AG's model to address two related questions:

- which treatment strategy is most cost effective in avoiding future OVEs in each of the four specified populations?

- how does the availability of generic clopidogrel at a lower price than the branded product affect the assessment of cost effectiveness of clopidogrel containing treatment strategies?

Detailed results are given in this section separately for each of the four populations previously defined, and using deterministic analyses.

6.4.1 IS only patients

Deterministic analysis

Table 6-38 and Table 6-39 summarise the main economic results obtained with the AG model for the IS patient population. Figure 6-4 to Figure 6-7 illustrate these findings in the form of a cost-effectiveness plane plot with cost-effectiveness frontier. The primary analysis (first block in Table 6-38 and Table 6-39 and Figure 6-4) reveals that only two strategies lie on the boundary, but neither of these involves initial use of clopidogrel. In all scenarios, the most cost-effective strategy begins with MRD+ASA, followed by ASA and finally clopidogrel.

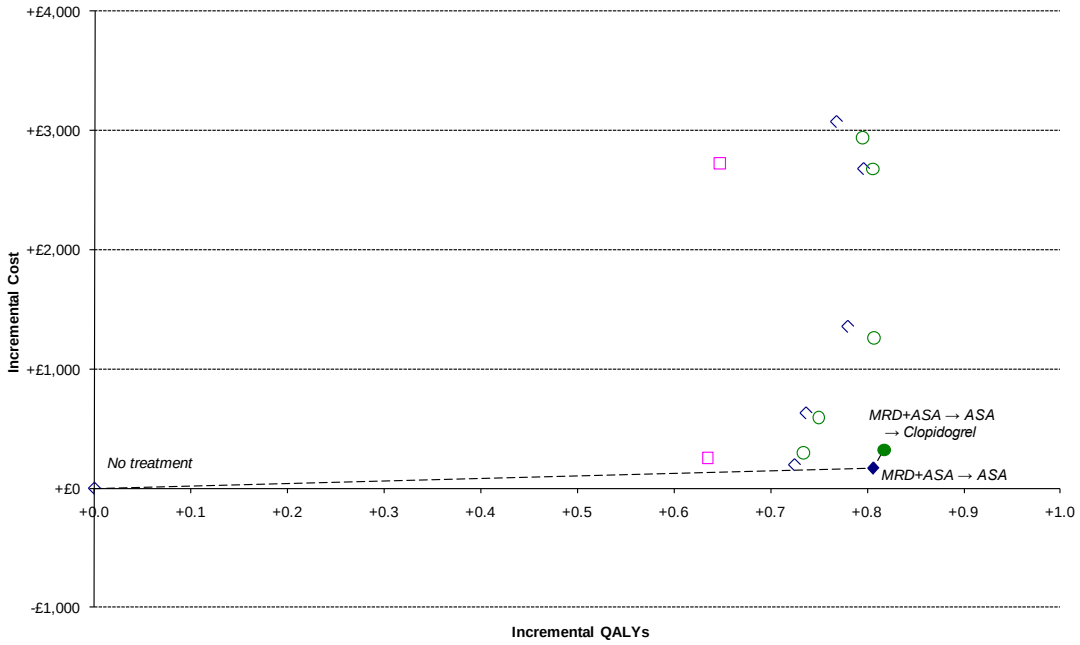

Figure 6-4 Cost-effectiveness plane and frontier showing available treatment strategies for 'IS only' patients (using MRD+ASA as per TA90 guidance)

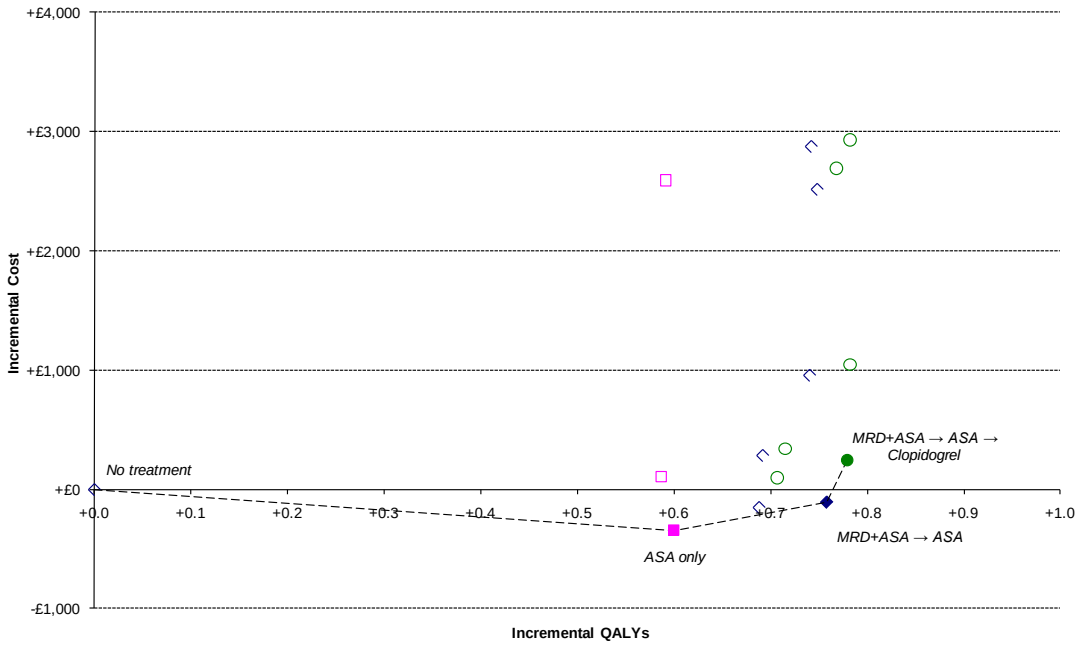

Figure 6-5 Cost-effectiveness plane and frontier showing available treatment strategies for 'IS only' patients (without applying TA90 guidance)

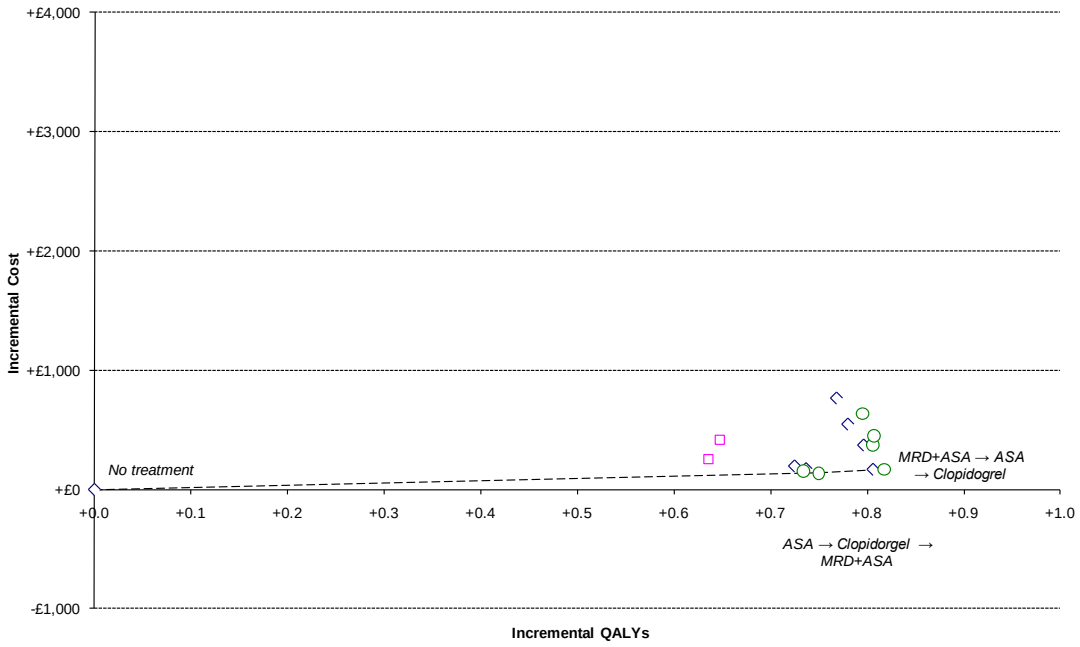

Figure 6-6 Cost-effectiveness plane and frontier showing available treatment strategies for 'IS only' patients (using MRD+ASA as per TA90 guidance and generic clopidogrel price)

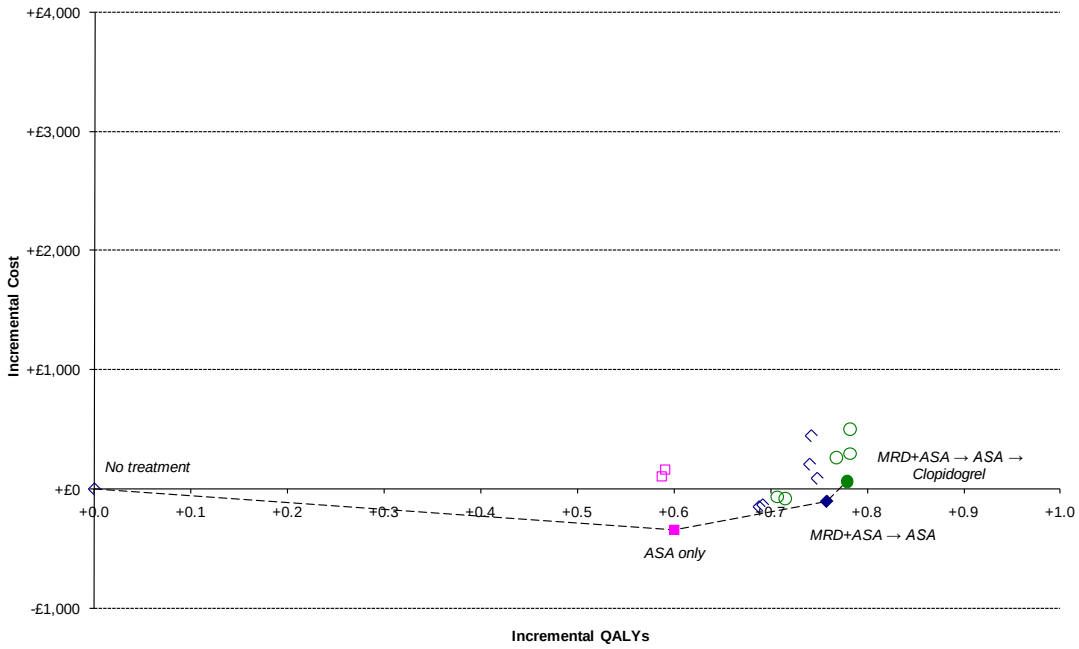

Figure 6-7 Cost-effectiveness plane and frontier showing available treatment strategies for 'IS only' patients (without applying TA90 guidance and using generic clopidogrel price)

Intolerance to ASA and/or MRD: In patients who are intolerant of ASA, clopidogrel and MRD are the only available long-term therapy options available, and only MRD may be used post-IS events as per TA90 guidance.[23] These are compared to the 'no treatment' scenario in Table 6-40 and indicate that clopidogrel followed by MRD is the most cost-effective approach to OVE prevention, independent of both TA90 guidance[23] and the price of clopidogrel.

For patients who are intolerant of MRD, only clopidogrel and ASA are available for long-tem therapy, and TA90 guidance[23] is not relevant (Table 6-41). In this instance the price of clopidogrel is important in determining cost effectiveness; at the branded price, the preferred strategy is ASA followed by clopidogrel, but for the generic price clopidogrel followed by ASA is more cost effective. For patients intolerant to both ASA and MRD, only clopidogrel is available for long-term prevention and is seen to be more cost effective than no preventive therapy.

Table 6-38 Deterministic results from AG model for treatment of the 'IS only' population

CLOP price	TA90 status	Strategy			Costs					Utility	Incremental analysis 1			Incremental analysis 2			Incremental analysis vs. 3		
		Tx 1	Tx 2	Tx 3	APT	Events	Cont. care	AE	Total	QALYs	IQ	IC	ICER	IQ	IC	ICER	IQ	IC	ICER
Full	MRD+ASA	None	None	None	£167	£9,085	£25,793	£32	£35,078	6.838									
		ASA	None	None	£844	£6,025	£19,899	£189	£26,956	6.156	-0.682	-£8,122	£11,915	-1.488	-£8,291	£5,573			
		Clop	None	None	£3,414	£7,185	£27,033	£173	£37,805	7.485	0.647	£2,726	£4,212	-0.159	£2,558	Dom			
		M+A	None	None	£784	£7,248	£27,150	£152	£35,334	7.473	0.635	£256	£403	-0.171	£87	Dom			
		ASA	Clop	None	£838	£7,140	£27,490	£241	£35,709	7.574	0.737	£631	£857	-0.069	£462	Dom			
		ASA	M+A	None	£321	£7,185	£27,532	£237	£35,275	7.562	0.725	£197	£272	-0.081	£28	Dom			
		Clop	ASA	None	£3,430	£6,810	£27,288	£228	£37,756	7.634	0.796	£2,677	£3,363	-0.010	£2,509	Dom			
		Clop	M+A	None	£3,619	£6,991	£27,328	£213	£38,150	7.606	0.768	£3,072	£3,999	-0.038	£2,903	Dom			
		M+A	ASA	None	£805	£6,784	£27,441	£218	£35,247	7.644	0.806	£169	£210						
		M+A	Clop	None	£1,948	£6,903	£27,376	£207	£36,434	7.618	0.780	£1,356	£1,739	-0.026	£1,187	Dom			
		ASA	Clop	M+A	£867	£7,046	£27,513	£246	£35,673	7.587	0.750	£595	£793	-0.056	£426	Dom			
		ASA	M+A	Clop	£507	£7,096	£27,526	£244	£35,373	7.572	0.734	£295	£402	-0.072	£126	Dom			
		Clop	ASA	M+A	£3,460	£6,741	£27,321	£234	£37,756	7.643	0.806	£2,678	£3,324	0.000	£2,509	Dom			
		Clop	M+A	ASA	£3,612	£6,834	£27,347	£228	£38,021	7.633	0.795	£2,943	£3,701	-0.011	£2,774	Dom			
		M+A	Clop	ASA	£1,941	£6,749	£27,426	£222	£36,338	7.644	0.806	£1,260	£1,562	0.001	£1,091	£2.1m			
		M+A	ASA	Clop	£1,010	£6,694	£27,469	£226	£35,399	7.655	0.817	£320	£392	0.011	£151	£13,567			
Full	Not used	None	None	None	£0	£8,887	£26,568	£0	£35,455	6.956									
		ASA	None	None	£62	£7,054	£27,803	£195	£35,113	7.556	0.600	-£342	-£570						
		Clop	None	None	£3,470	£7,010	£27,409	£158	£38,047	7.547	0.591	£2,592	£4,384	-0.008	£2,934	Dom			
		M+A	None	None	£698	£7,071	£27,657	£136	£35,561	7.543	0.587	£106	£181	-0.013	£448	Dom			
		ASA	Clop	None	£662	£6,907	£27,951	£222	£35,742	7.648	0.692	£287	£414	0.092	£628	£6,797	-0.066	£394	Dom
		ASA	M+A	None	£182	£6,908	£27,997	£218	£35,305	7.644	0.688	-£150	-£218	0.089	£192	£2,162	-0.070	-£42	£606
		Clop	ASA	None	£3,486	£6,637	£27,642	£209	£37,975	7.704	0.749	£2,520	£3,366	0.149	£2,862	£19,224	-0.009	£2,628	Dom
		Clop	M+A	None	£3,654	£6,783	£27,705	£193	£38,335	7.698	0.742	£2,880	£3,879	0.143	£3,222	£22,566	-0.016	£2,988	Dom
		M+A	ASA	None	£717	£6,611	£27,823	£196	£35,347	7.714	0.758	-£108	-£142	0.158	£234	£1,478			
		M+A	Clop	None	£1,769	£6,714	£27,747	£184	£36,415	7.697	0.741	£959	£1,295	0.141	£1,301	£9,226	-0.017	£1,067	Dom
		ASA	Clop	M+A	£706	£6,782	£28,076	£231	£35,795	7.671	0.715	£340	£476	0.115	£682	£5,911	-0.043	£448	Dom
		ASA	M+A	Clop	£411	£6,797	£28,113	£229	£35,550	7.663	0.707	£95	£134	0.107	£436	£4,067	-0.051	£202	Dom
		Clop	ASA	M+A	£3,535	£6,552	£27,841	£219	£38,147	7.724	0.768	£2,692	£3,505	0.168	£3,034	£18,015	0.010	£2,800	£278,165
		Clop	M+A	ASA	£3,660	£6,602	£27,911	£213	£38,386	7.738	0.782	£2,931	£3,748	0.182	£3,273	£17,954	0.024	£3,039	£126,862
		M+A	Clop	ASA	£1,776	£6,530	£27,992	£204	£36,502	7.738	0.782	£1,047	£1,338	0.182	£1,388	£7,618	0.024	£1,154	£48,244
		M+A	ASA	Clop	£979	£6,496	£28,019	£208	£35,702	7.735	0.779	£247	£317	0.179	£588	£3,282	0.021	£354	£16,894

IC, IQ = incremental cost & QALYs, ICER = incremental cost-effectiveness ratio, M+A = MRD+ASA, Dom = dominated, ICER in **bold** = strategy on cost-effectiveness frontier

Table 6-39 Deterministic results from AG model for treatment of the 'IS only' population (continued)

CLOP price	TA90 status	Strategy			Costs					Utility	Incremental analysis 1			Incremental analysis 2			Incremental analysis vs. 3		
		Tx 1	Tx 2	Tx 3	APT	Events	Cont. care	AE	Total	QALYs	IQ	IC	ICER	IQ	IC	ICER	IQ	IC	ICER
Generic	MRD+ASA	None	None	None	£167	£9,085	£25,793	£32	£35,078	6.838									
		ASA	None	None	£844	£6,025	£19,899	£189	£26,956	6.156	-0.682	-£8,122	£11,915	-1.431	-£8,260	£5,771			
		Clop	None	None	£1,109	£7,185	£27,033	£173	£35,500	7.485	0.647	£421	£651	-0.102	£284	Dom			
		M+A	None	None	£784	£7,248	£27,150	£152	£35,334	7.473	0.635	£256	£403	-0.115	£118	Dom			
		ASA	Clop	None	£381	£7,140	£27,490	£241	£35,253	7.574	0.737	£174	£237	-0.013	£36	Dom			
		ASA	M+A	None	£321	£7,185	£27,532	£237	£35,275	7.562	0.725	£197	£272	-0.025	£59	Dom			
		Clop	ASA	None	£1,125	£6,810	£27,288	£228	£35,451	7.634	0.796	£372	£468	0.047	£234	£5,020	-0.021	£203	Dom
		Clop	M+A	None	£1,314	£6,991	£27,328	£213	£35,845	7.606	0.768	£767	£998	0.019	£629	£33,699	-0.049	£597	Dom
		M+A	ASA	None	£805	£6,784	£27,441	£218	£35,247	7.644	0.806	£169	£210	0.056	£31	£548	-0.011	-£1	£75
		M+A	Clop	None	£1,140	£6,903	£27,376	£207	£35,626	7.618	0.780	£548	£703	0.030	£410	£13,517	-0.037	£378	Dom
		ASA	**Clop**	**M+A**	£411	£7,046	£27,513	£246	£35,216	7.587	0.750	£138	**£184**						
		ASA	M+A	Clop	£368	£7,096	£27,526	£244	£35,234	7.572	0.734	£156	£212	-0.015	£18	Dom			
		Clop	ASA	M+A	£1,155	£6,741	£27,321	£234	£35,451	7.643	0.806	£373	£463	0.056	£235	£4,191	-0.012	£203	Dom
		Clop	M+A	ASA	£1,307	£6,834	£27,347	£228	£35,716	7.633	0.795	£638	£802	0.046	£500	£10,983	-0.022	£468	Dom
		M+A	Clop	ASA	£1,133	£6,749	£27,426	£222	£35,530	7.644	0.806	£452	£561	0.057	£314	£5,518	-0.011	£282	Dom
		M+A	**ASA**	**Clop**	£860	£6,694	£27,469	£226	£35,248	7.655	0.817	£170	£208	0.068	£32	**£470**			
Generic	Not used	None	None	None	£0	£8,887	£26,568	£0	£35,455	6.956									
		ASA	None	None	£62	£7,054	£27,803	£195	£35,113	7.556	0.600	-£342	**-£570**						
		Clop	None	None	£1,041	£7,010	£27,409	£158	£35,618	7.547	0.591	£163	£275	-0.008	£504	Dom			
		M+A	None	None	£698	£7,071	£27,657	£136	£35,561	7.543	0.587	£106	£181	-0.013	£448	Dom			
		ASA	Clop	None	£242	£6,907	£27,951	£222	£35,322	7.648	0.692	-£134	-£193	0.092	£208	£2,251	-0.066	-£26	
		ASA	M+A	None	£182	£6,908	£27,997	£218	£35,305	7.644	0.688	-£150	-£218	0.089	£192	£2,162	-0.070	-£42	£606
		Clop	ASA	None	£1,057	£6,637	£27,642	£209	£35,545	7.704	0.749	£90	£121	0.149	£432	£2,902	-0.009	£198	Dom
		Clop	M+A	None	£1,224	£6,783	£27,705	£193	£35,905	7.698	0.742	£450	£607	0.143	£792	£5,548	-0.016	£558	Dom
		M+A	**ASA**	None	£717	£6,611	£27,823	£196	£35,347	7.714	0.758	-£108	-£142	0.158	£234	**£1,478**			
		M+A	Clop	None	£1,019	£6,714	£27,747	£184	£35,665	7.697	0.741	£210	£283	0.141	£551	£3,909	-0.017	£317	Dom
		ASA	Clop	M+A	£286	£6,782	£28,076	£231	£35,375	7.671	0.715	-£80	-£112	0.115	£261	£2,267	-0.043	£27	DOM
		ASA	M+A	Clop	£251	£6,797	£28,113	£229	£35,389	7.663	0.707	-£66	-£93	0.107	£276	£2,570	-0.051	£42	DOM
		Clop	ASA	M+A	£1,105	£6,552	£27,841	£219	£35,717	7.724	0.768	£262	£342	0.168	£604	£3,588	0.010	£370	£36,769
		Clop	M+A	ASA	£1,231	£6,602	£27,911	£213	£35,957	7.738	0.782	£501	£641	0.182	£843	£4,626	0.024	£609	£25,431
		M+A	Clop	ASA	£1,026	£6,530	£27,992	£204	£35,752	7.738	0.782	£297	£379	0.182	£638	£3,503	0.024	£404	£16,901
		M+A	**ASA**	**Clop**	£796	£6,496	£28,019	£208	£35,519	7.735	0.779	£64	£82	0.179	£405	£2,261	0.021	£171	**£8,171**

IC, IQ = incremental cost & QALYs, ICER = incremental cost-effectiveness ratio, M+A = MRD+ASA, Dom = dominated, ICER in **bold** = strategy on cost-effectiveness frontier

Table 6-40 Deterministic results from AG model for treatment of the 'IS only' population with intolerance to ASA

CLOP price	TA90 status	Strategy			Costs					Utility	Incremental analysis 1			Incremental analysis 2			Incremental analysis vs. 3		
		Tx 1	Tx 2	Tx 3	APT	Events	Cont. care	AE	Total	QALYs	IQ	IC	ICER	IQ	IC	ICER	IQ	IC	ICER
ASA intolerant																			
Full	MRD	None	None	None	£164	£9,365	£25,697	£47	£35,273	6.806									
	MRD	**Clop**	None	None	£3,433	£7,406	£26,954	£186	£37,979	7.463	0.657	£2,705	£4,120	0.288	£1,457	**£5,066**			
	MRD	**MRD**	None	None	£777	£8,779	£26,744	£223	£36,522	7.175	0.369	£1,248	**£3,384**						
	MRD	**Clop**	**MRD**	None	£3,639	£7,487	£27,328	£245	£38,698	7.534	0.728	£3,425	£4,707	0.359	£2,177	£6,069	0.071	£719	**£10,139**
	MRD	MRD	Clop	None	£1,933	£8,435	£27,062	£277	£37,706	7.335	0.528	£2,432	£4,605	0.159	£1,184	£7,435	-0.128	-£273	£2,126
Full	Not used	None	None	None	£0	£8,887	£26,568	£0	£35,455	6.956									
	Not used	**Clop**	None	None	£3,470	£7,010	£27,409	£158	£38,047	7.547	0.591	£2,592	£4,384	0.248	£1,143	**£4,604**			
	Not used	**MRD**	None	None	£670	£8,404	£27,638	£192	£36,905	7.299	0.343	£1,450	**£4,225**						
	Not used	**Clop**	**MRD**	None	£3,650	£7,099	£27,705	£209	£38,664	7.633	0.678	£3,209	£4,736	0.334	£1,759	£5,259	0.086	£616	**£7,142**
	Not used	MRD	Clop	None	£1,747	£8,029	£27,752	£241	£37,768	7.462	0.506	£2,313	£4,570	0.163	£864	£5,296	-0.085	-£279	£3,278
Generic	MRD	None	None	None	£164	£9,365	£25,697	£47	£35,273	6.806									
	MRD	**Clop**	None	None	£1,116	£7,406	£26,954	£186	£35,662	7.463	0.657	£388	**£591**						
	MRD	MRD	None	None	£777	£8,779	£26,744	£223	£36,522	7.175	0.369	£1,248	£3,384	-0.288	£860	Dom			
	MRD	**Clop**	**MRD**	None	£1,321	£7,487	£27,328	£245	£36,381	7.534	0.728	£1,108	£1,522	0.071	£719	**£10,139**			
	MRD	MRD	Clop	None	£1,127	£8,435	£27,062	£277	£36,900	7.335	0.528	£1,627	£3,080	-0.128	£1,239	Dom			
Generic	Not used	None	None	None	£0	£8,887	£26,568	£0	£35,455	6.956									
	Not used	**Clop**	None	None	£1,041	£7,010	£27,409	£158	£35,618	7.547	0.591	£163	**£275**						
	Not used	MRD	None	None	£670	£8,404	£27,638	£192	£36,905	7.299	0.343	£1,450	£4,225	-0.248	£1,287	Dom			
	Not used	**Clop**	**MRD**	None	£1,321	£7,487	£27,328	£245	£36,381	7.534	0.728	£1,108	£1,522	0.071	£719	**£10,139**			
	Not used	MRD	Clop	None	£1,127	£8,435	£27,062	£277	£36,900	7.335	0.528	£1,627	£3,080	-0.128	£1,239	Dom			

IC, IQ = incremental cost & QALYs, ICER = incremental cost-effectiveness ratio, Dom = dominated, ICER in **bold** = strategy on cost-effectiveness frontier, Cont. care = continuing care costs

Table 6-41 Deterministic results from AG model for treatment of the 'IS only' population with intolerance to MRD

CLOP price	TA90 status	Strategy			Costs					Utility	Incremental analysis 1			Incremental analysis 2			Incremental analysis vs. 3		
		Tx 1	Tx 2	Tx 3	APT	Events	Cont. care	AE	Total	QALYs	IQ	IC	ICER	IQ	IC	ICER	IQ	IC	ICER
MRD intolerant																			
Full	Not used	None	None	None	£0	£8,887	£26,568	£0	£35,455	6.956									
	Not used	ASA	None	None	£62	£7,054	£27,803	£195	£35,113	7.556	0.600	-£342	**-£570**						
	Not used	Clop	None	None	£3,470	£7,010	£27,409	£158	£38,047	7.547	0.591	£2,592	£4,384	-0.008	£2,934	Dom			
	Not used	ASA	Clop	None	£662	£6,907	£27,951	£222	£35,742	7.648	0.692	£287	£414	0.092	£628	**£6,797**			
	Not used	Clop	ASA	None	£3,486	£6,637	£27,642	£209	£37,975	7.704	0.749	£2,520	£3,366	0.149	£2,862	£19,224	0.056	£2,233	**£39,595**
Generic	Not used	None	None	None	£0	£8,887	£26,568	£0	£35,455	6.956									
	Not used	ASA	None	None	£62	£7,054	£27,803	£195	£35,113	7.556	0.600	-£342	**-£570**						
	Not used	Clop	None	None	£1,041	£7,010	£27,409	£158	£35,618	7.547	0.591	£163	£275	-0.008	£504	Dom			
	Not used	ASA	Clop	None	£242	£6,907	£27,951	£222	£35,322	7.648	0.692	-£134	-£193	0.092	£208	**£2,251**			
	Not used	Clop	ASA	None	£1,057	£6,637	£27,642	£209	£35,545	7.704	0.749	£90	£121	0.149	£432	£2,902	0.056	£224	**£3,970**
ASA & MRD intolerant																			
Full	Not used	None	None	None	£0	£8,887	£26,568	£0	£35,455	6.956									
	Not used	Clop	None	None	£3,470	£7,010	£27,409	£158	£38,047	7.547	0.591	£2,592	**£4,384**						
Generic	Not used	None	None	None	£0	£8,887	£26,568	£0	£35,455	6.956									
	Not used	Clop	None	None	£1,041	£7,010	£27,409	£158	£35,618	7.547	0.591	£163	£275						

IC, IQ = incremental cost & QALYs, ICER = incremental cost-effectiveness ratio, Dom = dominated, ICER in **bold** = strategy on cost-effectiveness frontier, Cont. care = continuing care costs

6.4.2 MI only patients

Deterministic analysis

Table 6-42 summarises the main economic results obtained with the AG model for the MI patient population. Figure 6-8 to Figure 6-11 illustrate these findings in the form of a cost-effectiveness plane plot with cost-effectiveness frontier. The primary analysis (first block in Table 6-42 and Figure 6-8) reveals that only two strategies lie on the boundary, but both strategies involving initial use of clopidogrel are dominated by those where ASA is the first treatment offered to 'MI only' patients (being both less effective and more expensive) regardless of whether or not TA90 guidance[23] is applied, or whether the generic price of clopidogrel is used. In all scenarios, the incremental cost effectiveness of allowing clopidogrel as a subsequent therapy after failure of ASA therapy compared to ASA treatment alone is less than £7,000 per QALY gained suggesting that ASA followed by clopidogrel may be the optimal strategy for this patient group.

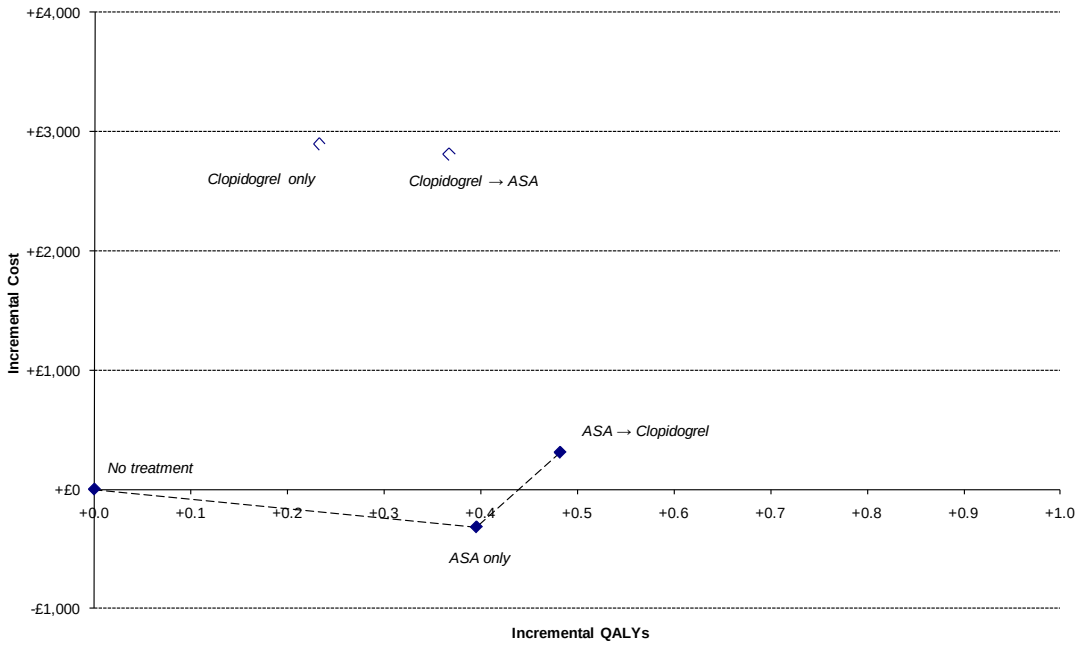

Figure 6-8 Cost-effectiveness plane and frontier showing available treatment strategies for 'MI only' patients (using MRD+ASA as per TA90 guidance)

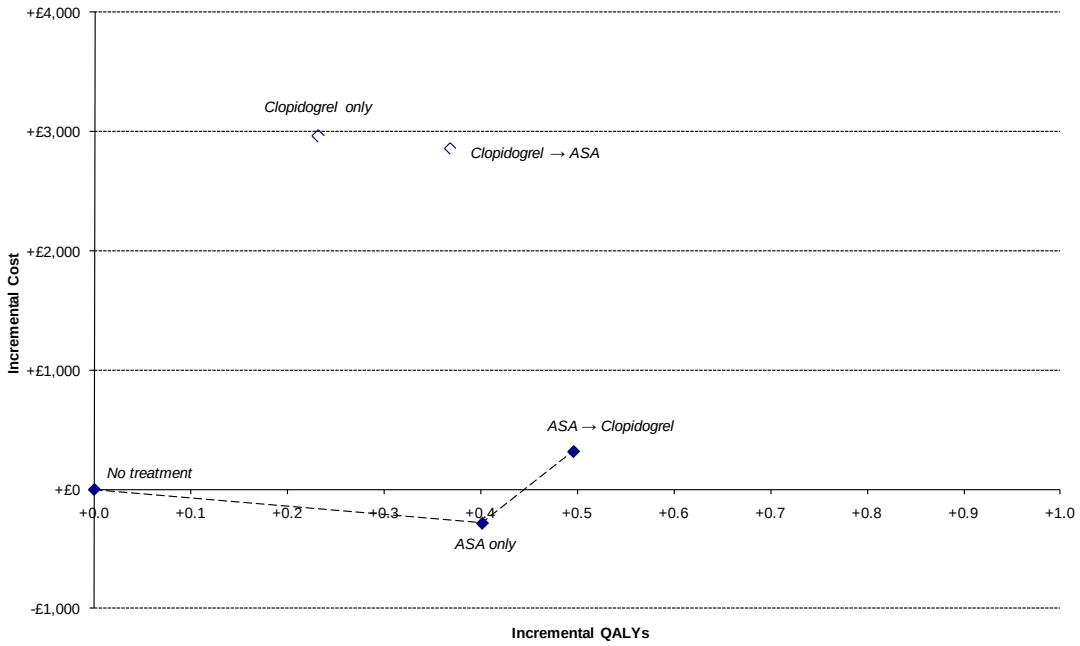

Figure 6-9 Cost-effectiveness plane and frontier showing available treatment strategies for 'MI only' patients (without applying TA90 guidance)

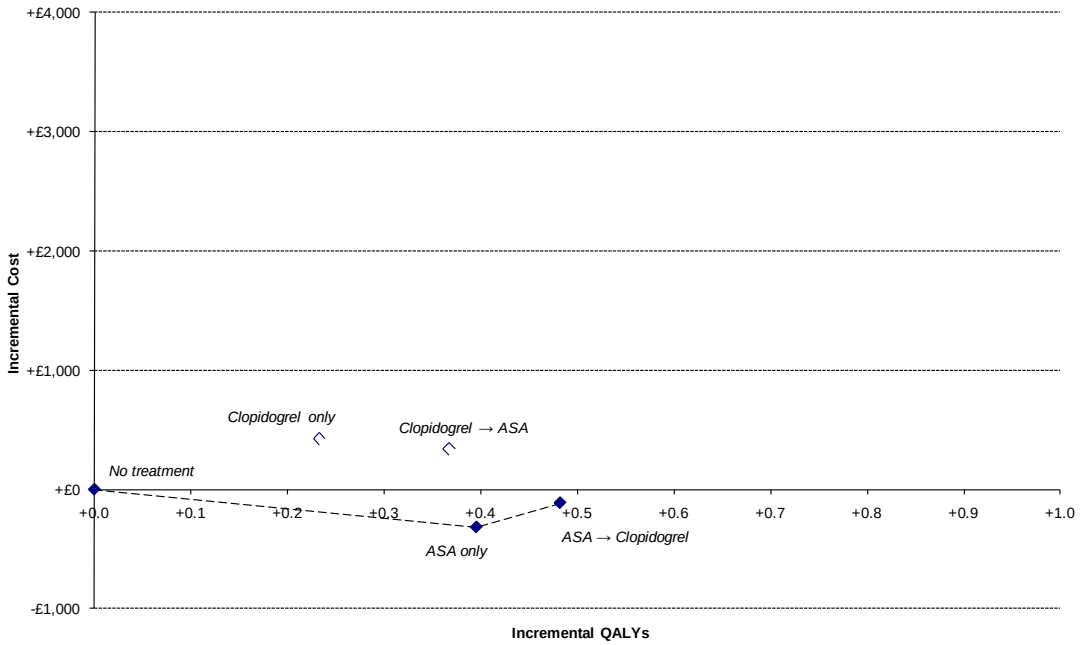

Figure 6-10 Cost-effectiveness plane and frontier showing available treatment strategies for 'MI only' patients (using MRD+ASA as per TA90 guidance and generic clopidogrel price)

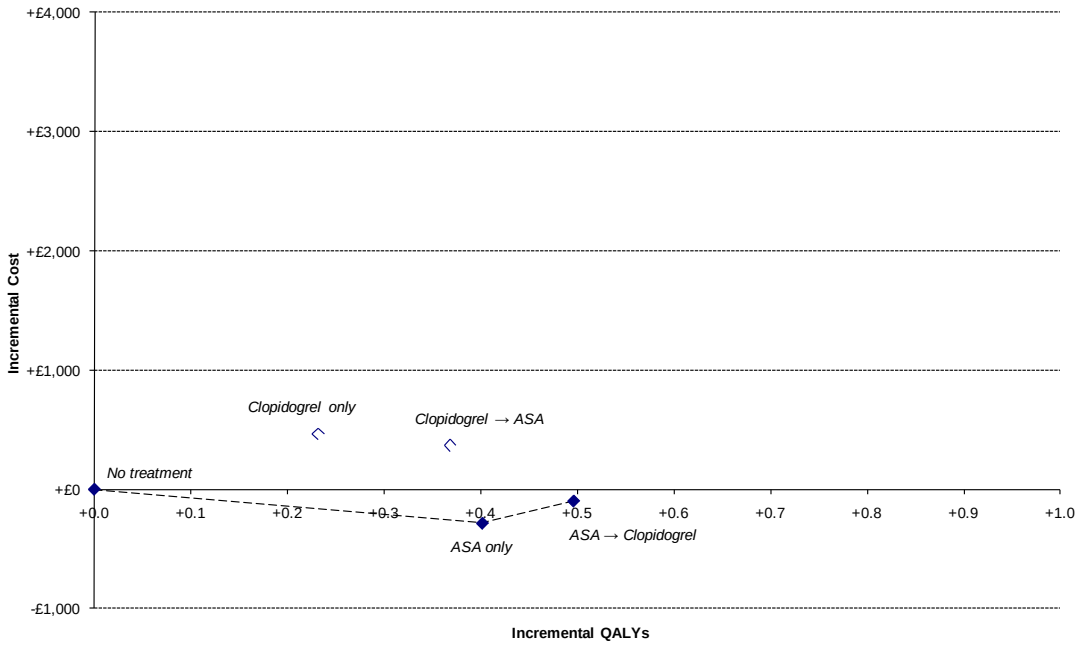

Figure 6-11 Cost-effectiveness plane and frontier showing available treatment strategies for 'MI only' patients (without applying TA90 guidance and using generic clopidogrel price)

Intolerance to ASA: In patients who are intolerant of ASA, clopidogrel is the only available long-term therapy available, and therefore comparisons have been carried out against the 'no treatment' scenario. The results are given in Table 6-43 and indicate that clopidogrel is a cost-effective approach to OVE prevention independent of both TA90 guidance[23] and the price of clopidogrel (ICERs ranging between £1,981 and £12,802 per QALY gained).

Table 6-42 Deterministic results from AG model for treatment of the 'MI only' population

CLOP price	TA90 status	Strategy			Costs					Utility	Incremental analysis vs. no ATP treatment			Incremental analysis vs. ASA only strategy		
		Tx 1	Tx 2	Tx 3	APT	Events	Cont. care	AE	Total	QALYs	IQ	IC	ICER	IQ	IC	ICER
Full	MRD+ASA	None	None	None	£28	£4,664	£7,036	£5	£11,733	9.122	0.000	£0	-	-	-	-
	MRD+ASA	ASA	None	None	£84	£3,998	£7,124	£209	£11,416	9.518	0.396	-£317	-£802	-	-	-
	MRD+ASA	Clop	None	None	£3,552	£3,842	£7,071	£164	£14,630	9.355	0.232	£2,897	£12,478	-0.163	£3,214	Dom
	MRD+ASA	ASA	Clop	None	£695	£3,928	£7,182	£237	£12,043	9.605	0.482	£310	£642	0.087	£627	£7,234
	MRD+ASA	Clop	ASA	None	£3,571	£3,655	£7,101	£220	£14,546	9.489	0.367	£2,813	£7,669	-0.029	£3,131	Dom
Full	Not used	None	None	None	£0	£4,708	£7,019	£0	£11,726	9.125	0.000	£0	-	-	-	-
	Not used	ASA	None	None	£65	£4,014	£7,158	£206	£11,443	9.526	0.401	-£283	-£706	-	-	-
	Not used	Clop	None	None	£3,567	£3,861	£7,102	£162	£14,692	9.357	0.232	£2,965	£12,802	-0.170	£3,249	Dom
	Not used	ASA	Clop	None	£660	£3,932	£7,220	£233	£12,045	9.620	0.496	£319	£643	0.094	£602	£6,381
	Not used	Clop	ASA	None	£3,584	£3,666	£7,123	£216	£14,589	9.493	0.368	£2,863	£7,784	-0.033	£3,146	Dom
Generic	MRD+ASA	None	None	None	£28	£4,664	£7,036	£5	£11,733	9.122	0.000	£0	-	-	-	-
	MRD+ASA	ASA	None	None	£84	£3,998	£7,124	£209	£11,416	9.518	0.396	-£317	-£802	-	-	-
	MRD+ASA	Clop	None	None	£1,079	£3,842	£7,071	£164	£12,157	9.355	0.232	£424	£1,828	-0.163	£742	Dom
	MRD+ASA	ASA	Clop	None	£272	£3,928	£7,182	£237	£11,620	9.605	0.482	-£113	-£234	0.087	£204	£2,357
	MRD+ASA	Clop	ASA	None	£1,099	£3,655	£7,101	£220	£12,074	9.489	0.367	£341	£930	-0.029	£658	Dom
Generic	Not used	None	None	None	£0	£4,708	£7,019	£0	£11,726	9.125	0.000	£0	-	-	-	-
	Not used	ASA	None	None	£65	£4,014	£7,158	£206	£11,443	9.526	0.401	-£283	-£706	-	-	-
	Not used	Clop	None	None	£1,070	£3,861	£7,102	£162	£12,194	9.357	0.232	£468	£2,020	-0.170	£751	Dom
	Not used	ASA	Clop	None	£244	£3,932	£7,220	£233	£11,628	9.620	0.496	-£98	-£198	0.094	£185	£1,964
	Not used	Clop	ASA	None	£1,087	£3,666	£7,123	£216	£12,092	9.493	0.368	£366	£994	-0.033	£649	Dom

Dom = dominated by another strategy

Table 6-43 Deterministic results from AG model for treatment of ASA-intolerant patients in the 'MI only' population

CLOP price	TA90 status	Strategy			Costs					Utility	ICER
		Tx 1	Tx 2	Tx 3	APT	Events	Cont. care	AE	Total	QALYs	£/QALY
Full	MRD	None	None	None	£28	£4,732	£7,060	£8	£11,828	9.118	
	MRD	Clop	None	None	£3,586	£3,906	£7,133	£168	£14,793	9.355	£12,523
Full	Not used	None	None	None	£0	£4,826	£7,019	£0	£11,726	9.125	
	Not used	Clop	None	None	£3,551	£3,975	£7,102	£162	£14,692	9.357	£12,802
Generic	MRD	None	None	None	£28	£4,732	£7,060	£8	£11,828	9.118	
	MRD	Clop	None	None	£1,090	£3,906	£7,133	£168	£12,297	9.355	£1,981
Generic	Not used	None	None	None	£0	£4,708	£7,019	£0	£11,726	9.125	
	Not used	Clop	None	None	£1,070	£3,861	£7,102	£162	£12,194	9.357	£2,020

6.4.3 PAD only patients

Deterministic analysis

Table 6-44 summarises the main economic results obtained with the AG model for the 'PAD only' patient population. Figure 6-12 to Figure 6-15 illustrate these findings in the form of a cost-effectiveness plane plot with cost-effectiveness frontier. The primary analysis (first block in Table 6-44 and Figure 6-12) reveals that three strategies lie on the boundary, but the clopidogrel only strategy in clearly less cost effective than all other options. This is true in all PAD scenarios. When the requirement is removed to adhere to TA90 guidance[23] following an IS event, the absolute values of costs and outcomes are modified, but the relativities between strategies remain qualitatively unchanged (Figure 6-13 and Figure 6-15). If the full branded price of clopidogrel is replaced by the NHS generic price, the cost differences between the strategies are markedly reduced, but the broad pattern is unchanged. In all scenarios the ICER for a strategy of clopidogrel followed by ASA when compared to ASA followed by clopidogrel appears to be well within the range considered cost effective (under £10,000 per QALY gained for branded clopidogrel and under £3,000 per QALY for generic clopidogrel), suggesting this as the optimal strategy for this patient group.

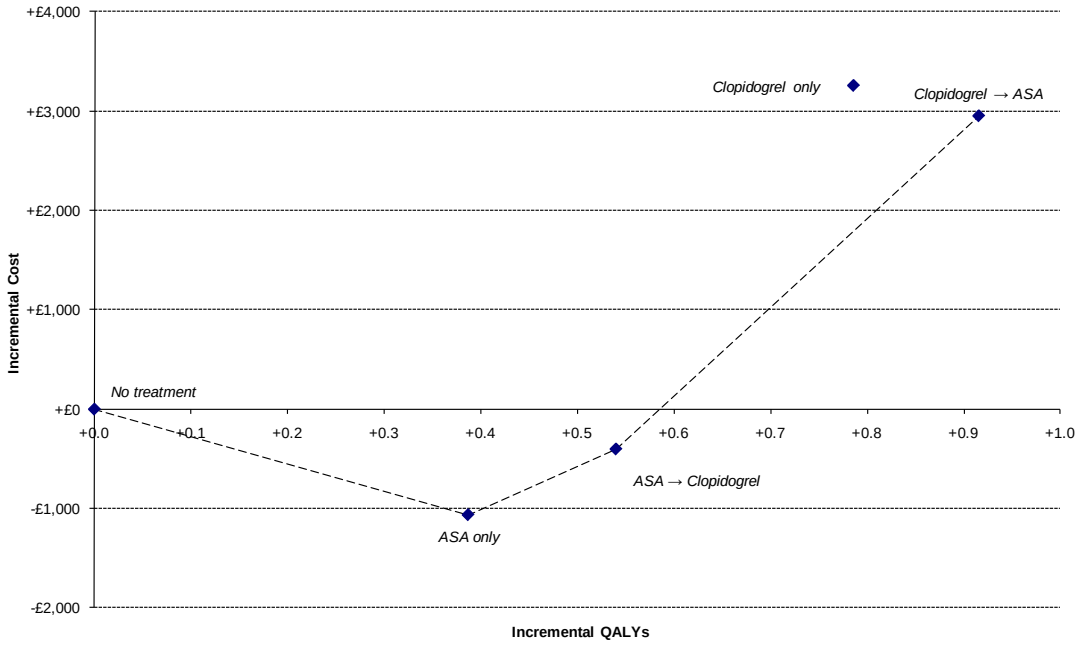

Figure 6-12 Cost-effectiveness plane and frontier showing available treatment strategies for 'PAD only' patients (using MRD+ASA as per TA90 guidance)

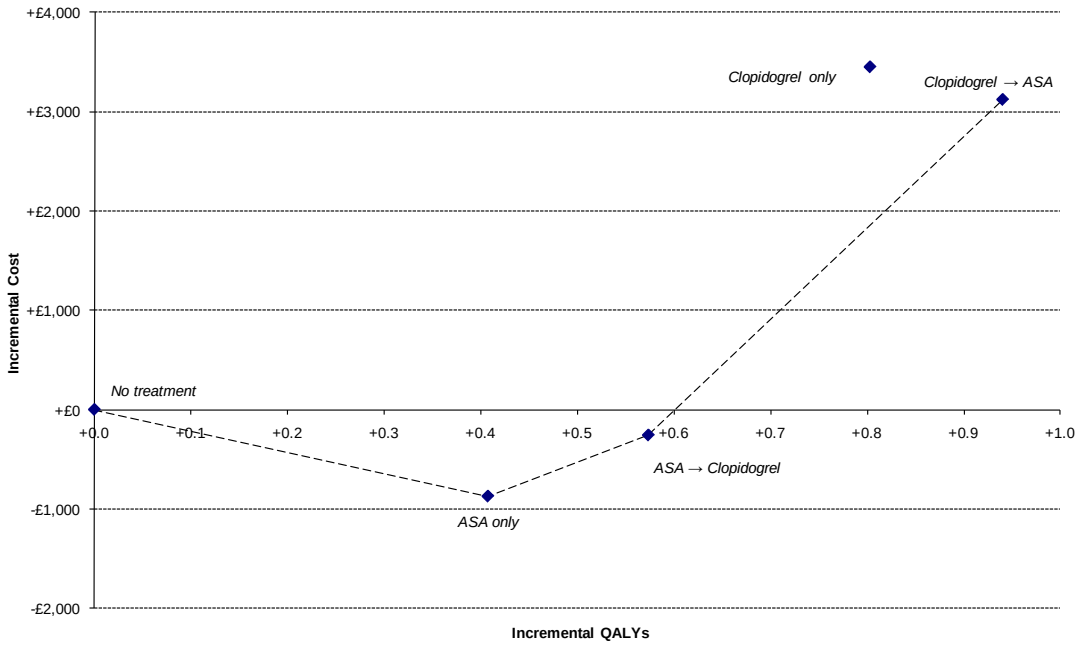

Figure 6-13 Cost-effectiveness plane and frontier showing available treatment strategies for 'PAD only' patients (without applying TA90 guidance)

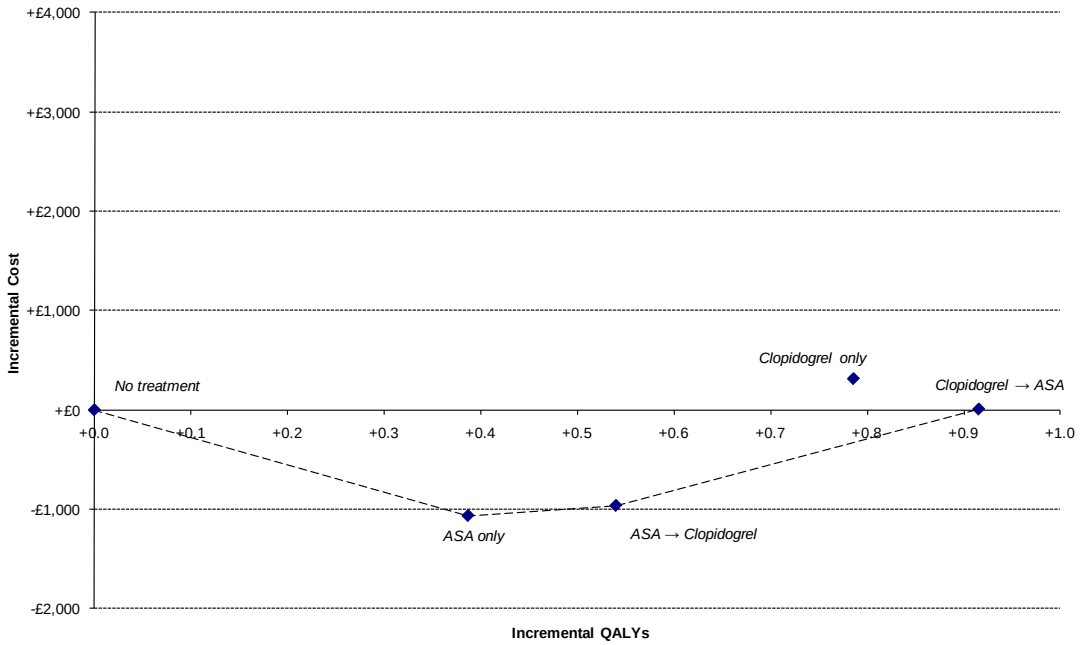

Figure 6-14 Cost-effectiveness plane and frontier showing available treatment strategies for 'PAD only' patients (using MRD+ASA as per TA90 guidance and generic clopidogrel price)

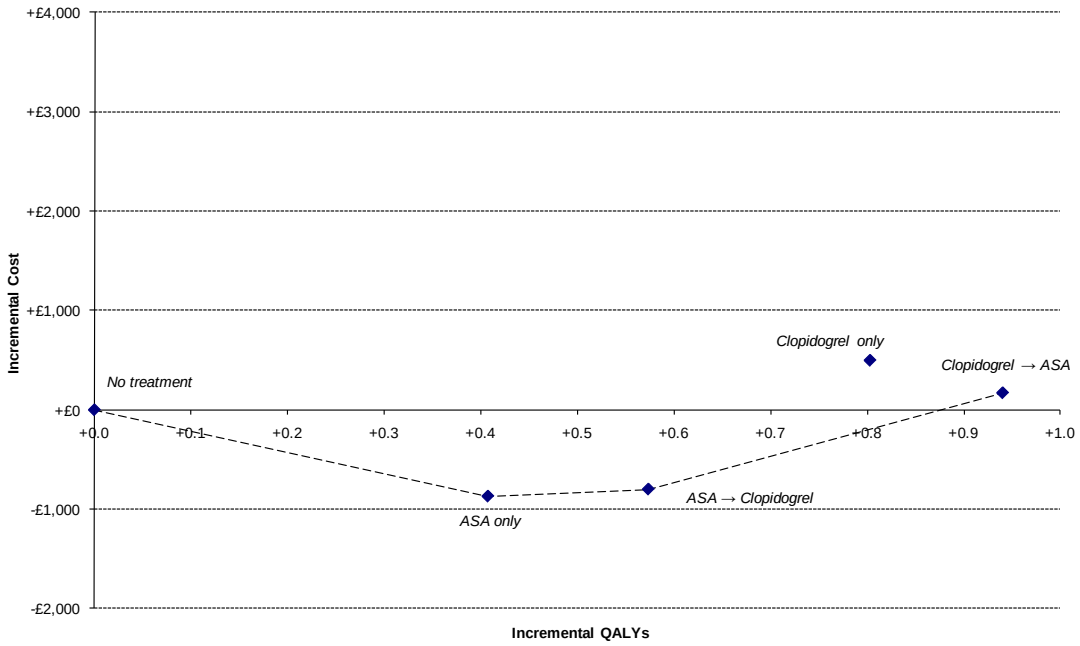

Figure 6-15 Cost-effectiveness plane and frontier showing available treatment strategies for 'PAD only' patients (without applying TA90 guidance and using generic clopidogrel price)

Intolerance to ASA: In patients who are intolerant of ASA, clopidogrel is the only available long-term therapy available, and therefore comparisons have been carried out against the 'no treatment' scenario. The results are given in Table 6-45 and indicate that clopidogrel is a cost-effective approach to OVE prevention independent of both TA90 guidance[23] and the price of clopidogrel.

Table 6-44 Deterministic results from AG model for treatment of the 'PAD only' population

CLOP price	TA90 status	Strategy			Costs					Utility	Incremental analysis vs. no ATP treatment			Incremental analysis vs. ASA only strategy			Incremental analysis vs. ASA → CLOP strategy		
		Tx 1	Tx 2	Tx 3	APT	Events	Cont. care	AE	Total	QALYs	IQ	IC	ICER	IQ	IC	ICER	IQ	IC	ICER
Full	MRD+ASA	None	None	None	£52	£4,572	£2,579	£10	£7,213	9.302	0.000	£0	-	-	-	-	-	-	-
	MRD+ASA	ASA	None	None	£109	£3,759	£2,282	£230	£6,379	9.694	0.391	-£833	-£2,103	-	-	-	-	-	-
	MRD+ASA	Clop	None	None	£4,232	£3,849	£2,419	£199	£10,698	10.087	0.785	£3,485	£4,442	0.393	£4,318	£10,980	0.245	£3,754	£15,298
	MRD+ASA	ASA	Clop	None	£908	£3,626	£2,144	£266	£6,944	9.842	0.539	-£269	-£498	0.148	£564	£3,816	-	-	-
	MRD+ASA	Clop	ASA	None	£4,250	£3,616	£2,184	£260	£10,310	10.211	0.909	£3,097	£3,407	0.518	£3,930	£7,591	0.370	£3,366	£9,102
Full	Not used	None	None	None	£0	£4,582	£2,568	£0	£7,150	9.305	0.000	£0	-	-	-	-	-	-	-
	Not used	ASA	None	None	£71	£3,713	£2,276	£225	£6,284	9.687	0.382	-£866	-£2,264	-	-	-	-	-	-
	Not used	Clop	None	None	£4,244	£3,802	£2,440	£193	£10,678	10.078	0.773	£3,528	£4,563	0.391	£4,394	£11,243	0.217	£3,747	£17,244
	Not used	ASA	Clop	None	£846	£3,611	£2,213	£260	£6,931	9.861	0.556	-£219	-£394	0.174	£647	£3,728	-	-	-
	Not used	Clop	ASA	None	£4,263	£3,598	£2,228	£253	£10,342	10.210	0.905	£3,192	£3,526	0.523	£4,058	£7,763	0.349	£3,411	£9,769
Generic	MRD+ASA	None	None	None	£52	£4,572	£2,579	£10	£7,213	9.302	0.000	£0	-	-	-	-	-	-	-
	MRD+ASA	ASA	None	None	£109	£3,759	£2,282	£230	£6,379	9.694	0.391	-£833	-£2,130	-	-	-	-	-	-
	MRD+ASA	Clop	None	None	£1,299	£3,849	£2,419	£199	£7,764	10.087	0.785	£552	£703	0.393	£1,385	£3,521	0.245	£1,379	£5,622
	MRD+ASA	ASA	Clop	None	£349	£3,626	£2,144	£266	£6,385	9.842	0.539	-£828	-£1,535	0.148	£6	£37	-	-	-
	MRD+ASA	Clop	ASA	None	£1,317	£3,616	£2,184	£260	£7,376	10.211	0.909	£164	£180	0.518	£997	£1,925	0.370	£991	£2,681
Generic	Not used	None	None	None	£0	£4,582	£2,568	£0	£7,150	9.305	0.000	£0	-	-	-	-	-	-	-
	Not used	ASA	None	None	£71	£3,713	£2,276	£225	£6,284	9.687	0.382	-£866	-£2,264	-	-	-	-	-	-
	Not used	Clop	None	None	£1,272	£3,802	£2,440	£193	£7,707	10.078	0.773	£557	£721	0.391	£1,423	£3,641	0.217	£1,319	£6,070
	Not used	ASA	Clop	None	£303	£3,611	£2,213	£260	£6,388	9.861	0.556	-£762	-£1,370	0.174	£104	£600	-	-	-
	Not used	Clop	ASA	None	£1,292	£3,598	£2,228	£253	£7,371	10.210	0.905	£221	£244	0.523	£1,087	£2,080	0.349	£983	£2,815

Table 6-45 Deterministic results from AG model for treatment of ASA-intolerant patients in the 'PAD only' population

CLOP price	TA90 status	Strategy			Costs					Utility	ICER
		Tx 1	Tx 2	Tx 3	APT	Events	Cont. care	AE	Total	QALYs	£/QALY
Full	MRD	None	None	None	£52	£4,640	£2,579	£15	£7,286	9.296	
	MRD	Clop	None	None	£4,256	£3,959	£2,497	£204	£10,915	10.086	£4,596
Full	Not used	None	None	None	£0	£4,582	£2,568	£0	£7,150	9.305	
	Not used	Clop	None	None	£4,244	£3,802	£2,440	£193	£10,678	10.078	£4,563
Generic	MRD	None	None	None	£52	£4,640	£2,579	£15	£7,286	9.296	
	MRD	Clop	None	None	£1,306	£3,959	£2,497	£204	£7,965	10.086	£861
Generic	Not used	None	None	None	£0	£4,582	£2,568	£0	£7,150	9.305	
	Not used	Clop	None	None	£1,272	£3,802	£2,440	£193	£7,707	10.078	£721

6.4.4 Patients with multivascular disease

Deterministic analysis

Table 6-46 summarises the main economic results obtained with the AG model for the MVD patient population. Figure 6-16 to Figure 6-19 illustrate these findings in the form of a cost-effectiveness plane plot with cost-effectiveness frontier. The primary analysis (first block in Table 6-46 and Figure 6-16) reveals that three strategies lie on the boundary, but the clopidogrel only strategy is clearly less cost effective than all other options. This is true in all MVD scenarios. When the requirement is removed to adhere to TA90 guidance[24] following an IS event, the absolute values of costs and outcomes are modified, but the relativities between strategies remain qualitatively unchanged (Figure 6-16 and Figure 6-18). If the full branded price of clopidogrel is replaced by the NHS generic price, the cost differences between the strategies are markedly reduced, but the broad pattern is unchanged. In all scenarios, clopidogrel followed by ASA is the most cost-effective strategy.

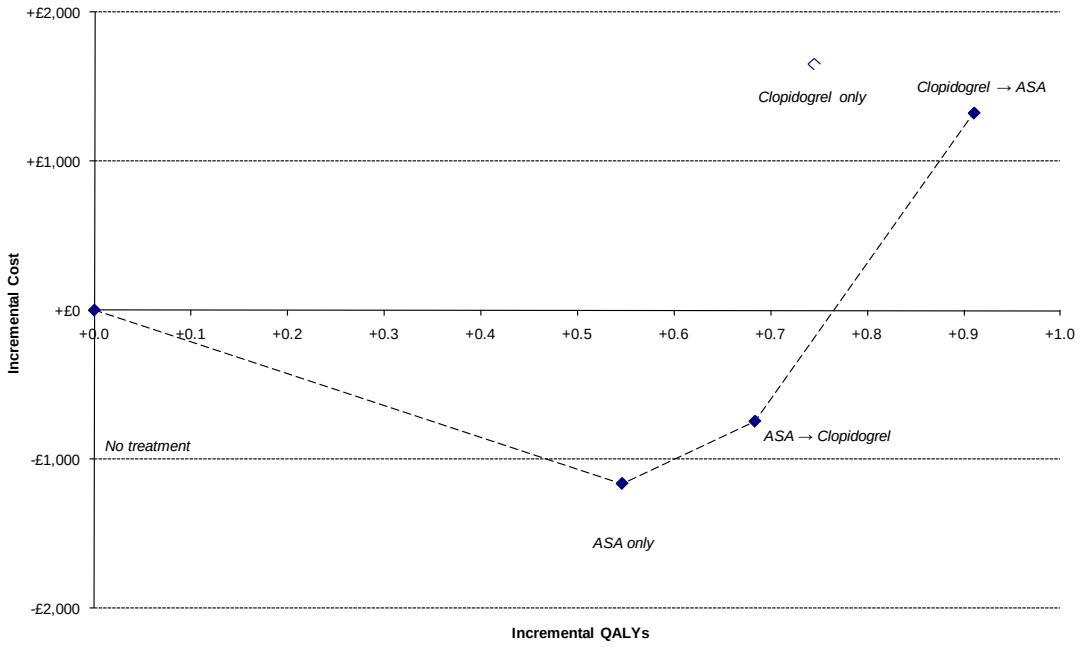

Figure 6-16 Cost-effectiveness plane and frontier showing available treatment strategies for MVD patients (using MRD+ASA as per TA90 guidance)

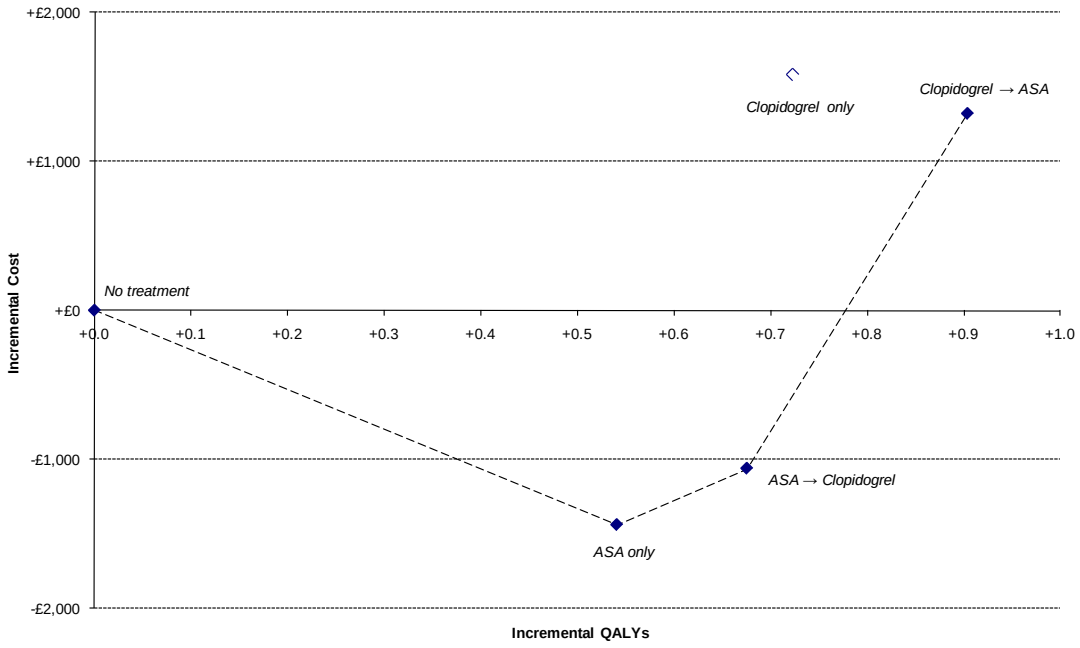

Figure 6-17 Cost-effectiveness plane and frontier showing available treatment strategies for MVD patients (without applying TA90 guidance)

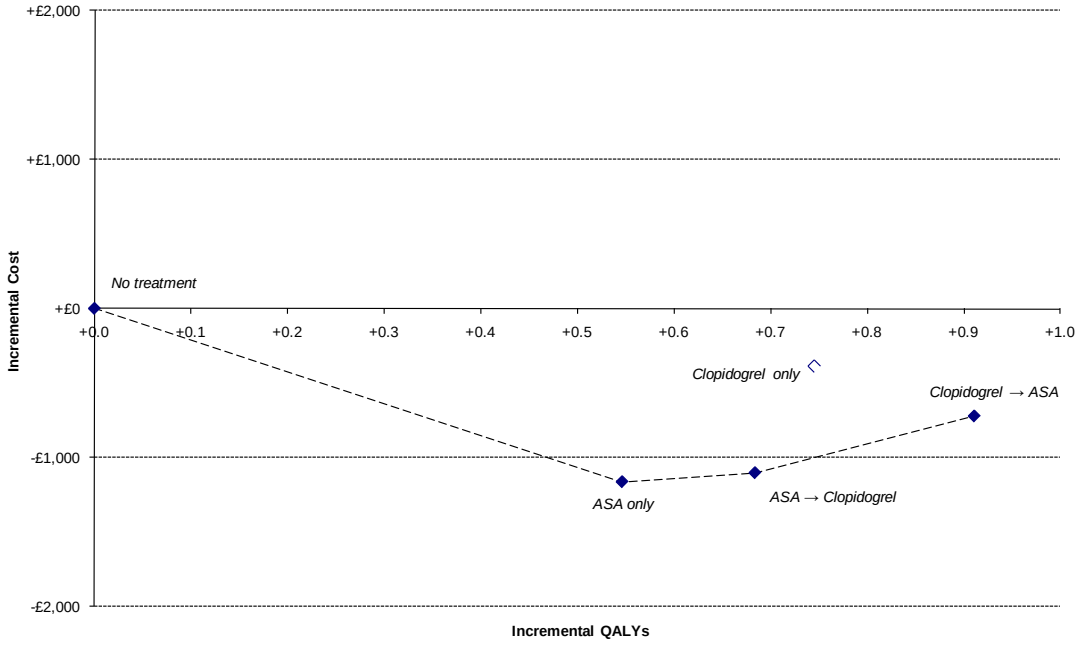

Figure 6-18 Cost-effectiveness plane and frontier showing available treatment strategies for MVD patients (using MRD+ASA as per TA90 guidance and generic clopidogrel price)

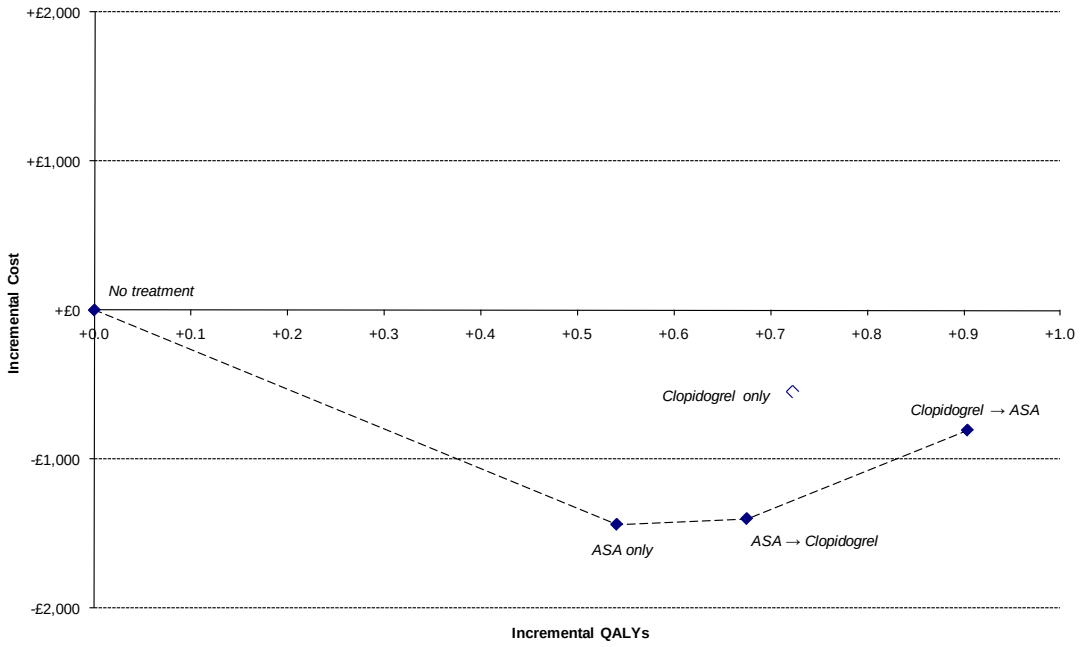

Figure 6-19 Cost-effectiveness plane and frontier showing available treatment strategies for MVD patients (without applying TA90 guidance and using generic clopidogrel price)

Intolerance to ASA: In patients who are intolerant of ASA, clopidogrel is the only long-term therapy available, and therefore comparisons have been carried out against the 'no treatment' scenario. The results are given in Table 6-47 and indicate that clopidogrel is a cost-effective approach to OVE prevention independent of both TA90 guidance[24] and the price of clopidogrel.

Table 6-46 Deterministic results from AG model for treatment of the MVD population

CLOP price	TA90 status	Strategy			Costs					Utility	Incremental analysis vs. no ATP treatment			Incremental analysis vs. ASA only strategy			Incremental analysis vs. ASA → CLOP strategy		
		Tx 1	Tx 2	Tx 3	APT	Events	Cont. care	AE	Total	QALYs	IQ	IC	ICER	IQ	IC	ICER	IQ	IC	ICER
Full	MRD+ASA	None	None	None	£127	£8,280	£12,156	£25	£20,587	5.377	0.000	£0	-	-	-	-	-	-	-
	MRD+ASA	ASA	None	None	£141	£6,842	£12,264	£178	£19,426	5.923	0.546	-£1,162	-£2,128	-	-	-	-	-	-
	MRD+ASA	Clop	None	None	£3,013	£6,655	£12,422	£151	£22,242	6.122	0.745	£1,655	£2,220	0.199	£2,816	£14,147	0.062	£2,399	£38,936
	MRD+ASA	ASA	Clop	None	£658	£6,603	£12,379	£203	£19,843	6.060	0.684	-£745	-£1,090	0.137	£417	£3,035	-	-	-
	MRD+ASA	Clop	ASA	None	£3,021	£6,267	£12,424	£197	£21,908	6.287	0.910	£1,321	£1,451	0.364	£2,483	£6,814	0.227	£2,066	£9,104
Full	Not used	None	None	None	£0	£8,361	£12,407	£0	£20,768	5.422	0.000	£0	-	-	-	-	-	-	-
	Not used	ASA	None	None	£53	£6,680	£12,429	£166	£19,328	5.963	0.541	-£1,440	-£2,663	-	-	-	-	-	-
	Not used	Clop	None	None	£3,041	£6,596	£12,574	£138	£22,349	6.145	0.723	£1,582	£2,189	0.182	£3,021	£16,611	0.047	£2,643	£55,919
	Not used	ASA	Clop	None	£539	£6,476	£12,504	£188	£19,706	6.098	0.675	-£1,061	-£1,571	0.135	£379	£2,813	-	-	-
	Not used	Clop	ASA	None	£3,055	£6,213	£12,639	£183	£22,090	6.326	0.904	£1,322	£1,463	0.363	£2,762	£7,607	0.228	£2,384	£10,432
Generic	MRD+ASA	None	None	None	£127	£8,280	£12,156	£25	£20,587	5.377	0.000	£0	-	-	-	-	-	-	-
	MRD+ASA	ASA	None	None	£141	£6,842	£12,264	£178	£19,426	5.923	0.546	-£1,162	-£2,128	-	-	-		-	-
	MRD+ASA	Clop	None	None	£971	£6,655	£12,422	£151	£20,200	6.122	0.745	-£388	-£520	0.199	£774	£3,889	0.062	£714	£11,585
	MRD+ASA	ASA	Clop	None	£302	£6,603	£12,379	£203	£19,486	6.060	0.684	-£1,101	-£1,611	0.137	£60	£440	-	-	-
	MRD+ASA	Clop	ASA	None	£979	£6,267	£12,424	£197	£19,866	6.287	0.910	-£721	-£792	0.364	£441	£1,210	0.227	£380	£1,676
Generic	Not used	None	None	None	£0	£8,361	£12,407	£0	£20,768	5.422	0.000	£0	-	-	-	-	-	-	-
	Not used	ASA	None	None	£53	£6,680	£12,429	£166	£19,328	5.963	0.541	-£1,440	-£2,663	-	-	-	-	-	-
	Not used	Clop	None	None	£912	£6,596	£12,574	£138	£20,220	6.145	0.723	-£547	-£758	0.182	£892	£4,906	0.047	£854	£18,073
	Not used	ASA	Clop	None	£198	£6,476	£12,504	£188	£19,366	6.098	0.675	-£1,402	-£2,075	0.135	£38	£284	-	-	-
	Not used	Clop	ASA	None	£926	£6,213	£12,639	£183	£19,961	6.326	0.904	-£807	-£893	0.363	£633	£1,744	0.228	£595	£2,604

Table 6-47 Deterministic results from AG model for treatment of ASA-intolerant patients in the MVD population

CLOP price	TA90 status	Strategy			Costs					Utility	ICER
		Tx 1	Tx 2	Tx 3	APT	Events	Cont. care	AE	Total	QALYs	£/QALY
Full	MRD	None	None	None	£121	£8,429	£11,946	£35	£20,530	5.339	-
	MRD	Clop	None	None	£3,004	£6,835	£12,262	£160	£22,262	6.095	£2,290
Full	Not used	None	None	None	£0	£8,361	£12,407	£0	£20,768	5.422	-
	Not used	Clop	None	None	£3,041	£6,596	£12,574	£138	£22,349	6.145	£2,189
Generic	MRD	None	None	None	£121	£8,429	£11,946	£35	£20,530	5.339	-
	MRD	Clop	None	None	£970	£6,835	£12,262	£160	£20,228	6.095	-£400
Generic	Not used	None	None	None	£0	£8,361	£12,407	£0	£20,768	5.422	-
	Not used	Clop	None	None	£912	£6,596	£12,574	£138	£20,220	6.145	-£758

6.4.5 Univariate sensitivity analysis

The AG model incorporates 197 parameters involving estimation uncertainty for which their potential influence on the economic results should be examined. Carrying out a comprehensive assessment of each parameter individually was judged to be impractical (due to model running time involved) and largely uninformative. Instead, the parameters were grouped into 11 sets which were assessed collectively, taking the maxima of the reasonable value range of all members of a group as a basis for estimating one extreme scenario, and the minima for the other. This is likely to overstate the net effect of the individual factors, since it is very unlikely that all uncertainties within a group will be biased in the same direction. Nonetheless it was considered a helpful approach to identifying which broad categories of parameters have a greater likelihood of influencing an assessment of cost effectiveness through parameter uncertainty. In effect this approach defines an upper limit on the net influence of uncertainty in all the variables within the group.

Wherever possible the testing intervals have been set to the conventional 95% confidence interval for estimating the parameter value. In the few instances where this information was not available, a general range of +/- 10% of the central estimate was adopted. The latter was used for the duration of effect of the transient component of some event risks (known to have a minimal influence on model results), several events and continuing care costs, and to allow a notional uncertainty to be applied to the assumption, discussed above, that no additional weighting was necessary to the risk of non-vascular mortality in this population.

IS only population

Sensitivity analysis was carried out on the comparison of between the strategy recommended above (MRD+ASA followed by ASA followed by clopidogrel) and the de facto current 'standard care' of ASA using the branded price of clopidogrel and without TA90 guidance[23] applied. This scenario exhibits a deterministic ICER of £4,260 per QALY gained.

Figure 6-20 shows the results for each group of parameters. In most cases there is very little variation from the central ICER estimate. There are two exceptions: 'Key event risks' shows a comparatively larger uncertainty (though still well within the range normally considered acceptable), and the asymmetric range for 'antiplatelet cessation risks' indicating the inherent non-linearity of the model in this feature.

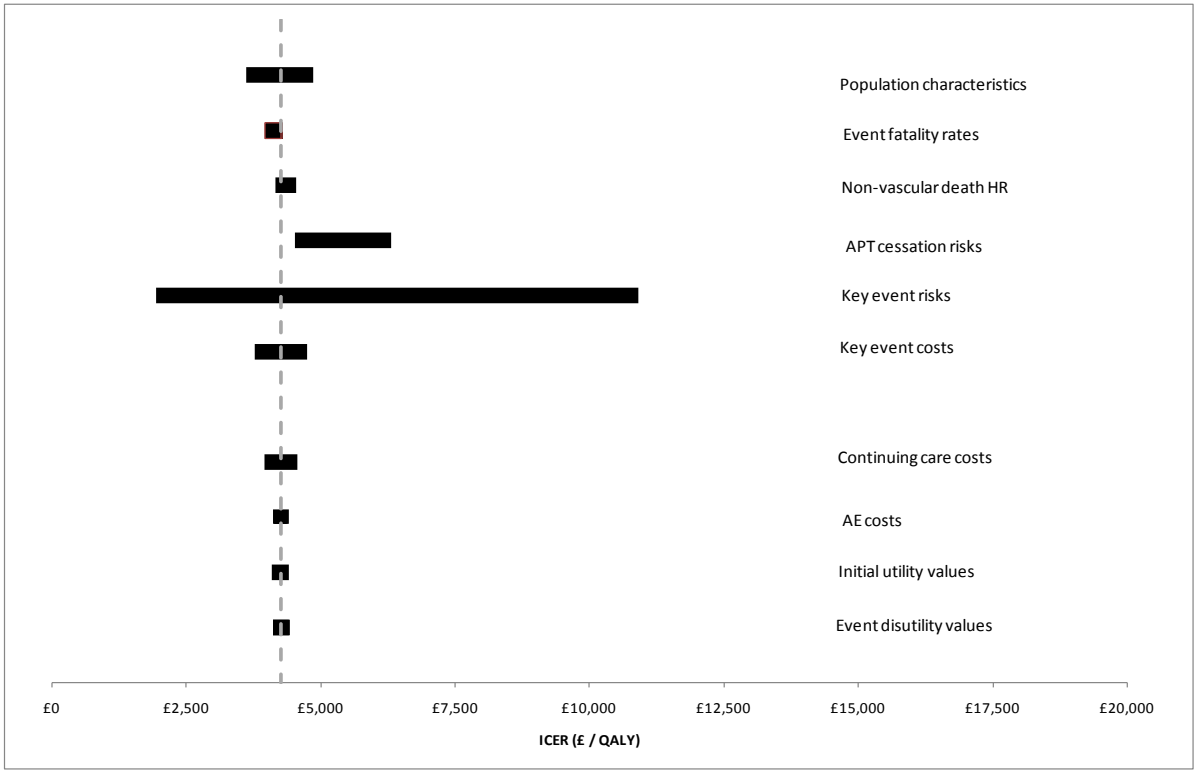

Figure 6-20 Sensitivity analysis for groups of model parameters for a comparison of the recommended strategy for 'IS only' patients (MRD+ASA -> ASA -> clopidogrel) vs ASA alone (branded price of clopidogrel/TA90 guidance not applied)

MI only population

Sensitivity analysis was carried out on the comparison of between the strategy recommended above (ASA followed by clopidogrel) and the de facto current 'standard care' of ASA using the branded price of clopidogrel and without TA90 guidance[23] applied. This scenario exhibits a deterministic ICER of £6,381 per QALY gained.

Figure 6-21 shows the results for each group of parameters. In most cases there is very little variation from the central ICER estimate. In this case the largest uncertainty is associated with antiplatelet treatment cessation risks, and to a lesser extent to event fatality rates. However, in all cases the ICER remains well below £10,000 per QALY gained.

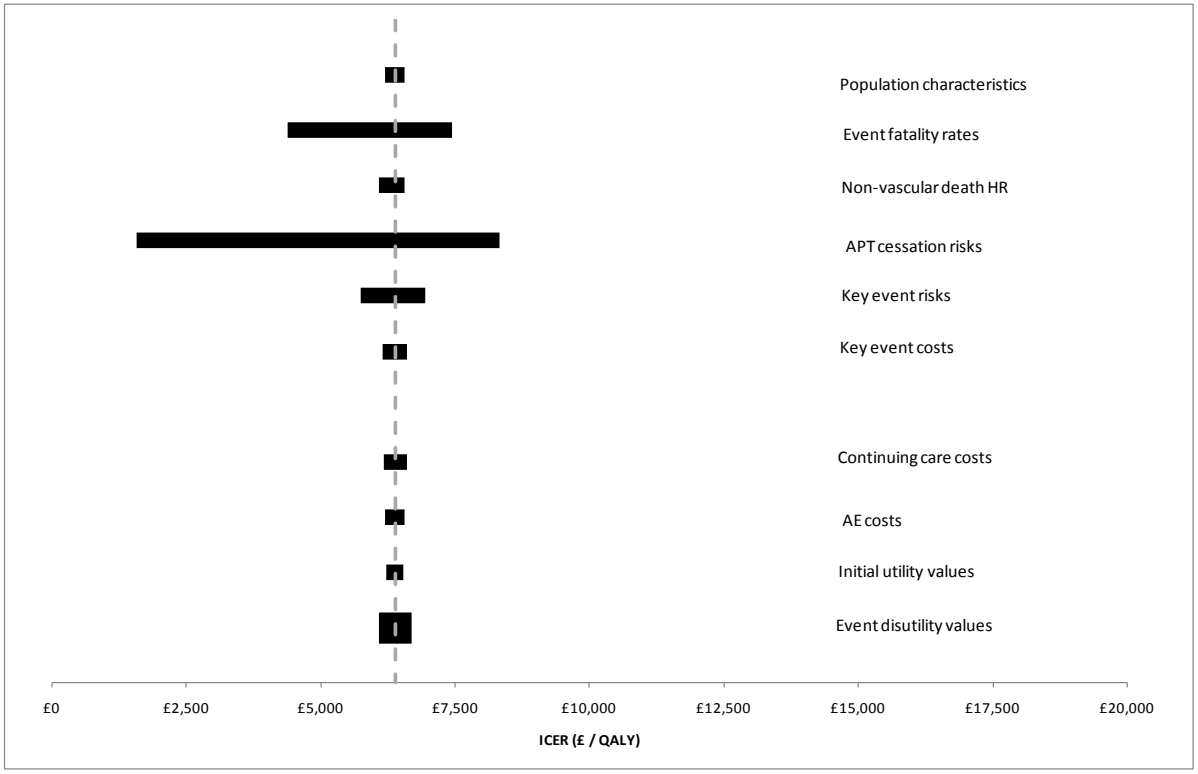

Figure 6-21 Sensitivity analysis for groups of model parameters for a comparison of the recommended strategy for 'MI only' patients (ASA -> clopidogrel) vs ASA alone (branded price of clopidogrel/TA90 guidance not applied)

PAD only population

Sensitivity analysis was carried out on the comparison of between the strategy recommended above (ASA followed by clopidogrel) and the de facto current 'standard care' of ASA, using the branded price of clopidogrel and without TA90 guidance[23] applied. This scenario exhibits a deterministic ICER of £6,381 per QALY gained.

Figure 6-22 shows the results for each group of parameters. In most cases there is very little variation from the central ICER estimate. However, a very large uncertainty range is associated with key event risks. Examination of the underlying parameter values points to a very few instances where there is evidence of a clear advantage for clopidogrel over ASA in this patient group, and where a benefit is indicated the lower confidence limits are closely aligned. As explained above, this effect may in fact be an artefact of the grouping of parameters in this analysis and can only be resolved through full probabilistic sensitivity analysis (provided in the addendum to follow).

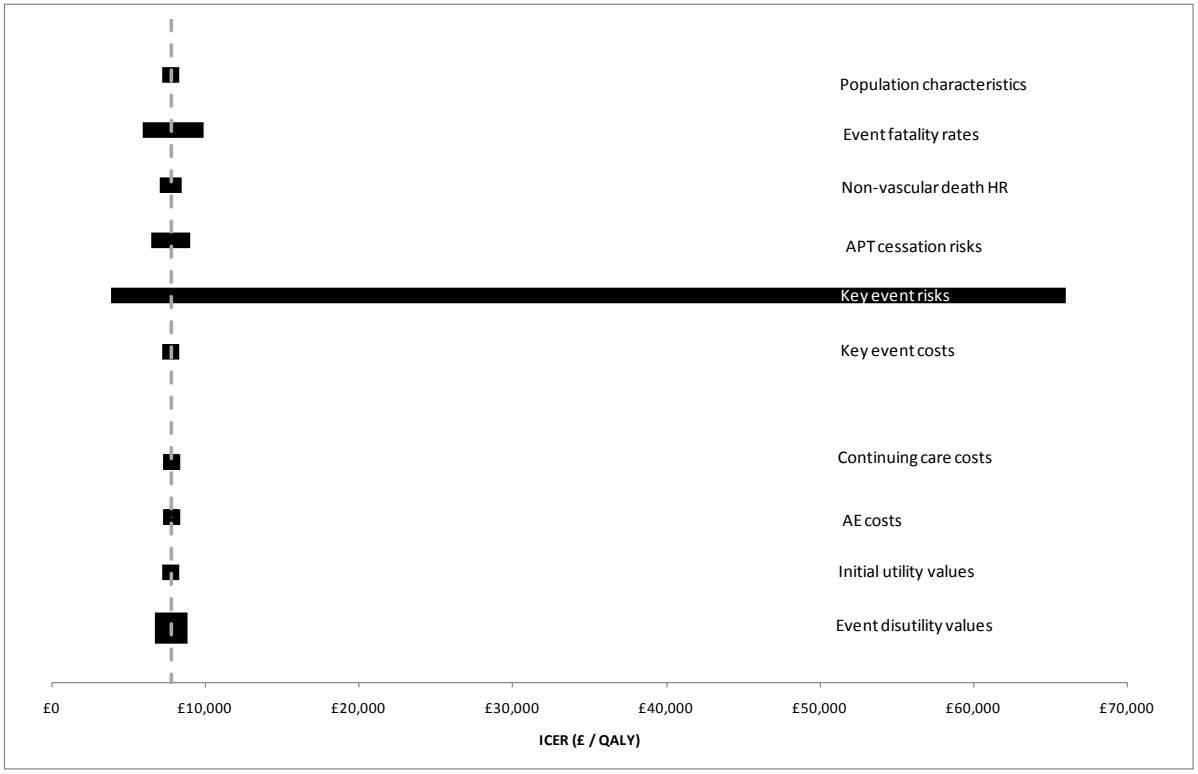

Figure 6-22 Sensitivity analysis for groups of model parameters for a comparison of the recommended strategy for 'PAD only' patients (ASA -> clopidogrel) vs ASA alone (branded price of clopidogrel/TA90 guidance not applied)

MVD population

Sensitivity analysis was carried out on the comparison of between the strategy recommended above (ASA followed by clopidogrel) and the de facto current 'standard care' of ASA using the branded price of clopidogrel and without TA90 guidance[23] applied. This scenario exhibits a deterministic ICER of £7,607 per QALY gained.

Figure 6-23 shows the results for each group of parameters. In most cases there is very little variation from the central ICER estimate. Exceptions are the event fatality rates group, and antiplatelet treatment cessation risks. However, in all cases the ICER remains below £11,000 per QALY gained.

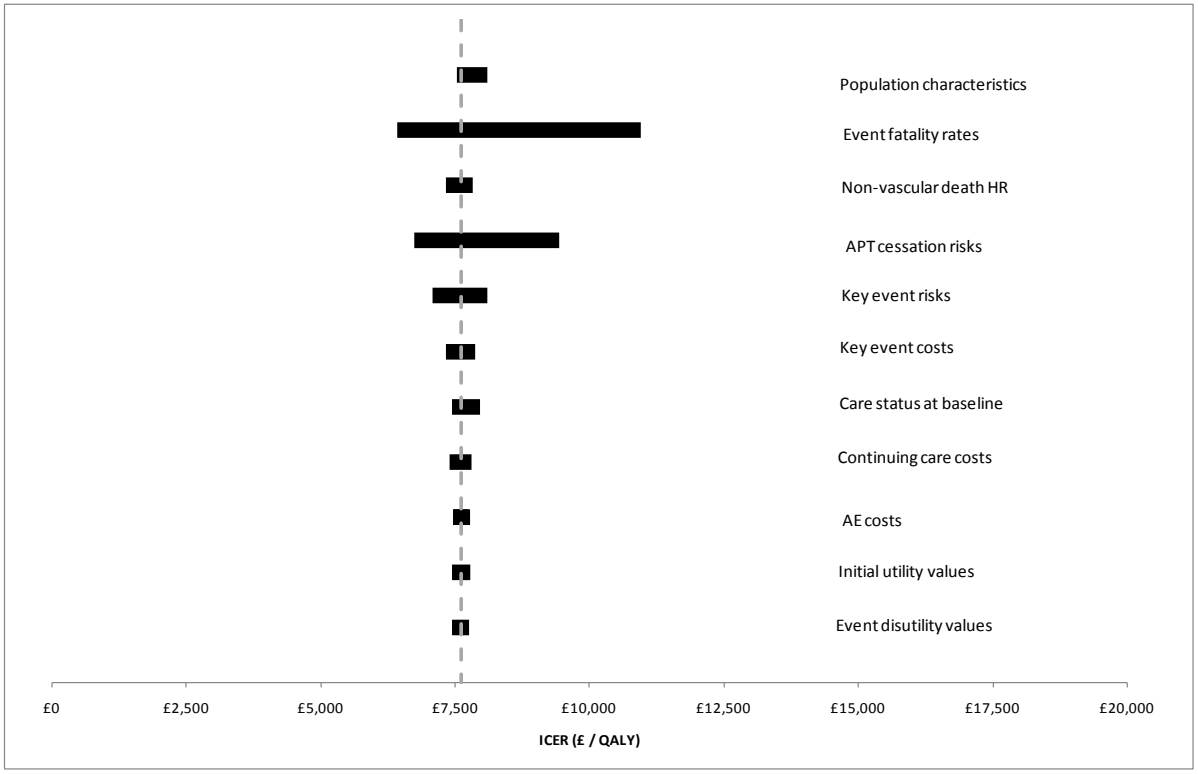

Figure 6-23 Sensitivity analysis for groups of model parameters for a comparison of the recommended strategy for MVD patients (ASA -> clopidogrel) vs ASA alone (branded price of clopidogrel/TA90 guidance not applied)

6.4.6 Summary of univariate results

These SAs allow the most likely sources of influential uncertainty to be identified. Firstly, there is no indication that cost and utility parameters, population characteristics or non-vascular mortality give rise to significant uncertainty in economic results. Secondly, three types of parameter are implicated in at least one of the SAs as likely to be influential on model results – the risk of events occurring, the fatality of such events, and the likelihood that patients will cease taking the prescribed preventive medications. Thirdly, model results for the 'PAD only' population appear to be particularly vulnerable to uncertainty in event risks, which should be addressed probabilistically (provided in the addendum to follow).

6.5 Summary of cost-effective strategies from Assessment Group economic model

The economic results described above are summarised in terms of preferred long-term preventive treatment strategies in Table 6-48. In only one circumstance (MRD intolerance in the 'IS only' patient) is the pricing of clopidogrel a determining factor in the choice of strategy.

Table 6-48 Summary table of optimal treatment strategy for each patient population obtained from deterministic analysis using the AG model

Clopidogrel price	TA90 guidance	Patient population			
		IS only	MI only	PAD only	MVD
No intolerances					
Branded	Applied	MRD+ASA → ASA → Clop	ASA → Clop	Clop → ASA	Clop → ASA
Branded	Not applied	MRD+ASA → ASA → Clop	ASA → Clop	Clop → ASA	Clop → ASA
Generic	Applied	MRD+ASA → ASA → Clop	ASA → Clop	Clop → ASA	Clop → ASA
Generic	Not applied	MRD+ASA → ASA → Clop	ASA → Clop	Clop → ASA	Clop → ASA
ASA intolerant					
Branded	Applied	Clop → MRD	Clop	Clop	Clop
Branded	Not applied	Clop → MRD	Clop	Clop	Clop
Generic	Applied	Clop → MRD	Clop	Clop	Clop
Generic	Not applied	Clop → MRD	Clop	Clop	Clop
MRD intolerant					
Branded	N/A	ASA → Clop	N/A	N/A	N/A
Generic	N/A	Clop → ASA	N/A	N/A	N/A
ASA & MRD intolerant					
	N/A	Clop	N/A	N/A	N/A
	N/A	Clop	N/A	N/A	N/A

CLOP= clopidogrel; ASA= aspirin; MRD= modified-release dipyridamole; N/A= not applicable; IS= ischaemic stroke; MI= myocardial infarction; PAD= peripheral arterial disease; MVD= multivascular disease

7 DISCUSSION

7.1 Statement of principal findings

The purpose of this report is to assess the clinical effectiveness and cost effectiveness of (i) clopidogrel and (ii) MRD alone or MRD+ASA compared with ASA and, where appropriate with each other, in the prevention of OVEs in patients with a history of MI or IS/TIA or established PAD. The final scope issued by NICE also called for consideration of the effectiveness of clopidogrel in patients with MVD.

7.1.1 Clinical effectiveness: direct evidence

Patients with MI and established PAD

Only the CAPRIE[25] trial offers evidence of the effectiveness of clopidogrel (versus ASA) in patients with prior history of MI or established PAD. For the whole population (patients with a prior history of MI or IS or established PAD), the CAPRIE[25] trial favoured clopidogrel; statistically significant outcomes were noted for the primary outcome (first occurrence of IS, MI or vascular death). However, the benefit appeared to be small and the boundaries of the confidence intervals raise the possibility that clopidogrel is not more beneficial than ASA across the patient population as a whole. When the results for each of the subgroups were analysed, there was a statistically significant effect only in patients with PAD (favouring clopidogrel).

Patients with MVD

The clinical effectiveness of clopidogrel in patients with MVD is assessed using data from three distinct sources: original CAPRIE[25] publication, a post-hoc analysis based on the CAPRIE[25] population and the AG's reclassification of the original patient groups using additional CAPRIE[25] data provided by the manufacturer. The results of all subgroup analyses undertaken suggest that patients with MVD are likely to experience elevated risks of future single and composite events and that treatment with clopidogrel is preferred over ASA.

Patients IS/TIA

For the IS/TIA population, clinical data are available from four studies: CAPRIE,[25] ESPS-2,[29] ESPRIT[55] and PRoFESS.[56] In the CAPRIE[25] trial there were no statistically significant differences in primary outcome between the treatment groups (MI, IS, PAD) in patients with prior history of IS. In ESPS-2[29] there was no difference in outcomes when MRD was compared with ASA; there was a statistically significant reduction in incidence of stroke in favour of MRD+ASA compared with ASA and MRD alone. No other primary outcome (all cause death; stroke and/or all cause death) showed statistically significant differences between any two treatment arms. In ESPRIT,[55] on the primary outcome (first occurrence of death from all vascular causes, non-fatal stroke, non-fatal MI, or major bleeding complication), the risk

of event occurrence was statistically significantly lower in the MRD+ASA arm compared to the ASA arm. In PRoFESS,[56] the rate of recurrent stroke of any type (primary outcome) was similar in the MRD+ASA and clopidogrel groups and the null hypothesis (that MRD+ASA is inferior to clopidogrel) could not be rejected.

In summary, the clinical evidence appears to suggest that MRD+ASA is preferred to MRD alone and ASA in patients with a prior history of IS/TIA. There is not enough clinical evidence to make an informed decision regarding the use of MRD+ASA vs clopidogrel in patients with a prior history of IS/TIA.

Adverse events

It is difficult to summarise the findings related to AEs, as the classification of these outcomes differed greatly across the trials; this was especially apparent for "bleeding" events. However, upon investigation, the AG did not identify any unexpected AEs associated with any of the drugs, bleeding was associated with ASA and headache was associated with MRD.

7.1.2 Clinical effectiveness: indirect evidence

7.1.3 IS/TIA populations only

There were no major differences in the results of the MTC and the direct estimates from head-to-head trials. However, two of five newly generated comparisons did yield statistically significant results: MRD alone had an increased risk of recurrent stroke when compared with clopidogrel; clopidogrel had fewer major bleeding events compared with ASA. Due to the small numbers of trials involved in the MTC and the forced selection of limited outcomes, caveats apply to the results. Findings were also based on patient populations in which there is no differentiation between patients with vascular disease in a single bed and those with MVD. The results of the indirect analyses, although confirmatory of the direct results, must therefore be interpreted with caution.

7.1.4 Cost-effectiveness evidence

Summary of previously published cost-effectiveness analyses

All of the economic evaluations except three[70, 71, 77] were published prior to 2006; this means more recent trials and clinical papers have not been used to inform the economic evaluations. The relevance of this review to decision making is therefore limited as the economic evaluations are not based on the most up-to-date clinical data. Nonetheless, the results of the literature review of cost-effectiveness evidence, show that, from a health service perspective, the use of clopidogrel in patients with previous PAD, IS or MI is a cost-effective option compared with ASA in the secondary prevention of OVEs. However, it is noted that Schleinitz et al[74] conclude that the evidence available to them at the time did not support increased efficacy of clopidogrel in the MI patient group; this is the only evaluation which includes subgroup analysis to estimate ICERs by patients' previous event. The combination of MRD+ASA seems to be cost effective compared with any other treatment in patients with previous IS/TIA in the secondary prevention of OVEs. There is only one evaluation which includes this combination (MRD+ASA) and therefore the evidence base is limited.

Summary of industry-submitted economic evaluations

Both manufacturers submitted *de novo* economic analyses which met the NICE reference case criteria.

Boehringer-Ingleheim is the manufacturer of MRD+ASA and the MS appears to demonstrate that:

(i) MRD+ASA (first line) and ASA (second line) is cost effective compared to ASA alone (£5,377 per QALY gained) and to no treatment (£5,910 per QALY gained) in patients with a history of IS/TIA

(ii) MRD+ASA (first line) and ASA (second line) compared with clopidogrel yields an ICER of £114,628 per QALY gained (patients with a history of IS) and ICER of £199,149 (patients with a history of TIA)

The main critique of the Boehringer-Ingleheim MS is focussed on the fact that the transition probabilities during the first four years for the MRD+ASA and clopidogrel arms are derived from PRoFESS,[56] ESPS-2[29] and ESPRIT[55] trials, beyond this point the manufacturers have used the same transition probability as used for the last six monthly cycle. This is an unreliable basis for long-term projection since close to the end of the trial patient numbers and the number of events are much reduced. As a consequence estimated incidence rates are very volatile and should not be relied on to drive the major part of the model calculations. It is important to note that the manufacturers used plavix (branded clopidogrel) at a price of £36.35 for 30 tablets (75mg) in the MS; the price of clopidogrel is now set at £10.90 for 30 tablets (75mg). This means that for the IS/TIA populations, clopidogrel is now cheaper and more effective compared with MRD+ASA.

Sanofi-aventis/Bristol-Myers Squibb are the manufacturers of clopidogrel and the MS appears to demonstrate that:

(i) For patients with a prior history of IS, clopidogrel is dominated by MRD+ASA and that clopidogrel vs MRD yields an ICER of £5,850 per QALY gained

(ii) For patients with a prior history of MI, clopidogrel vs ASA yields an ICER of £20,662 per QALY gained

(iii) For patients with established PAD, clopidogrel vs ASA yields an ICER of £18,845 per QALY gained

(iv) For patients with MVD, clopidogrel vs ASA yields an ICER of £15,524 per QALY gained.

The main critique of the Sanofi-aventis/Bristol-Myers Squibb economic model is focussed on the approach used to project health outcomes. The model assumes different transition probabilities every year until year three. Beyond this point the last-cycle transition probabilities are used for the remainder of the time horizon from year 3 to 35. This is an unreliable basis for long-term projection since close to the end of the trial patient numbers and the number of events are much reduced. As a consequence estimated incidence rates are very volatile and should not be relied on to drive the major part of the model calculations. It is important to note that using the new generic price of clopidogrel in the economic model improves the cost effectiveness of clopidogrel.

Summary of the Assessment Group's cost-effectiveness analysis

Cost-effectiveness results have been generated from the AG's economic model to address two related questions:

- which treatment strategy is most cost effective in avoiding future OVEs in each of the four specified populations?

- how does the availability of generic clopidogrel at a lower price than the branded product affect the assessment of cost effectiveness of clopidogrel containing treatment strategies?

Patients with IS/TIA:

- In all scenarios, the most cost-effective strategy begins with MRD+ASA, followed by ASA and finally clopidogrel
- In patients who are intolerant of ASA, compared to no treatment, clopidogrel followed by MRD is the most cost-effective approach, independent of both TA90 guidance[23] and the price of clopidogrel
- In patients who are intolerant of MRD, at the branded price, the preferred strategy is ASA followed by clopidogrel, but for the generic price clopidogrel followed by ASA is more cost effective
- For patients intolerant to both ASA and MRD, only clopidogrel is available for long-term prevention and is seen to be more cost effective than no preventive therapy.

Patients with MI:

- In all scenarios, the incremental cost effectiveness of allowing clopidogrel as a subsequent therapy after failure of ASA therapy compared to ASA treatment alone is less than £7,000 per QALY gained suggesting that ASA followed by clopidogrel may be the optimal strategy for this patient group
- In patients who are intolerant of ASA, clopidogrel is a cost-effective approach independent of both TA90 guidance[23] and the price of clopidogrel (ICERs ranging between £1,981 and £12,802 per QALY gained).

Patients with established PAD:

- In all scenarios the ICER for a strategy of clopidogrel followed by ASA when compared to ASA followed by clopidogrel appears to be well within the range considered cost effective (under £10,000 per QALY gained for branded clopidogrel and under £3,000 per QALY for generic clopidogrel), suggesting this as the optimal strategy for this patient group
- In patients who are intolerant to ASA, clopidogrel is a cost-effective approach independent of both TA90 guidance[23] and the price of clopidogrel.

Patients with MVD:

- In all scenarios, the incremental cost effectiveness of clopidogrel followed by ASA is the most cost-effective approach, independent of both TA90 guidance[23] and the price of clopidogrel
- In patients who are intolerant to ASA, clopidogrel is a cost-effective approach to OVE prevention independent of both TA90 guidance[23] and the price of clopidogrel.

7.1.5 Sensitivity analysis

The SAs undertaken using the AG's *de novo* model allow the most likely sources of influential uncertainty to be identified. Firstly, there is no indication that cost and utility parameters, population characteristics or non-vascular mortality give rise to significant uncertainty in economic results. Secondly, three types of parameter are implicated in at least one of the sensitivity analyses as likely to be influential on model results – the risk of events occurring, the fatality of such events, and the likelihood that patients will cease taking the prescribed preventive medications. Thirdly, model results for the 'PAD only' population appear to be particularly vulnerable to uncertainty in event risks, which should be addressed probabilistically.

7.2 Strengths and limitations

The key strengths of the report are threefold.

Firstly, the AG was able to consider the clinical and cost effectiveness of clopidogrel in people with MVD as specified in the final scope issued by NICE. Using information provided by the manufacturer, the AG re-analysed previously published data from the CAPRIE[25] trial and estimated the clinical and cost effectiveness of clopidogrel in this clinically important subgroup of patients. The AG confirmed the findings of other published clinical papers that patients with MVD are often at high risk of single and composite future clinical events.

Secondly, the AG did not simply address the short-term costs and benefits associated with clopidogrel and MRD; the clinical and cost effectiveness of clopidogrel and MRD is

considered over time using treatment scenarios. The strength of this approach is that it reflects the real world in which many patients will need to switch between different treatments during their lifetime. Restricting the analysis of costs and benefits of long-term prophylaxis to a few years frequently results in erroneous conclusions.

Finally, the structure of the economic model required to address the questions posed in the final scope issued by NICE necessitated careful planning and execution by the AG as well as access to further analyses of clinical data from the manufacturers. Working collaboratively, the AG was able to make best use of limited evidence and estimate relevant ICERs for individual patient populations using an economic model designed to minimise the scope for multiple cumulative bias inherent in long-term projection of multiple competing risks.

The clinical and cost-effectiveness findings of the report are limited by the nature of the clinical evidence available. For the MI, PAD and MVD patient populations, data were only available from the CAPRIE[25] trial (clopidogrel vs ASA) and the clinical results favoured clopidogrel. However, use of a single trial to generate clinical evidence for three individual patient populations inevitably attracts criticism. It is also important to note that the CAPRIE[25] trial did not distinguish between patients with NSTEMI and STEMI and this clearly inhibits the interpretation of the trial results for these clinically important subgroups of patients. For the IS/TIA population, relevant evidence was available from four published RCTs to inform the AG's assessment of clopidogrel and MRD. However, the studies were all very different in terms of design, patient populations and clinical outcomes, so that even indirect comparisons proved to be fraught with difficulty. The key comparison of interest for patients with IS/TIA was clopidogrel vs MRD+ASA and the results of this trial were inconclusive. This is unfortunate as it is unlikely that a trial of this design will ever be repeated. In summary, the clinical evidence available, particularly for MI, PAD and MVD populations, to answer the key questions set out in the final scope is limited.

7.3 Uncertainties

The findings of this report for the MI, PAD and MVD patient populations are reliant on several post-hoc subgroup analyses from a single trial; this means that there is inevitable uncertainty associated with the findings of this report. During the AC meeting which lead to the publication of TA90,[23] the AC "...was persuaded that undue reliance on subgroup analysis was inadvisable principally because of insufficient study power. Consequently, it was considered inappropriate to rely on post-hoc analyses..." However, the AG is of the opinion that reliance on the results of post-hoc subgroup analyses from a single trial was unavoidable if the questions set out in the final scope issued by NICE were to be adequately addressed in this report. To illustrate: there are clinical data available from PRoFESS,[56] CAPRIE,[25] ESPS-2[29] and ESPRIT[55] for the IS/TIA population, but the only clinical data available for patients

with prior MI, PAD and MVD is from the CAPRIE[25] trial. Patients with MI, PAD and MVD are not considered to constitute a single homogeneous clinical population; this means that use of subgroup analysis to estimate the clinical and cost effectiveness of clopidogrel for these individual subpopulations although not ideal is necessary. It is important to note that the size of each of the subgroup populations is considerable (IS= 4,740; MI= 5,741; PAD= 3,713; MVD= 4,991), and proved sufficient to demonstrate important differences in risk profiles between these groups.

In the absence of any universally agreed definition, the MVD subgroup analyses were based on a population defined by the AG. The AG's definition appears to be consistent with the simplest and broadest definition described in the published literature; however, it is likely that any differences in definitions of MVD subgroups will lead to differences in patient numbers and relative risks.

Additionally, the head to head trials and the MTC results have included subgroups of patients who had disease in more than one vascular bed as none of the trials distinguished between patients with single and multivascular disease.

8 CONCLUSIONS

For patients with IS/TIA, MRD+ASA followed by ASA followed by clopidogrel appears to be a cost-effective approach to the prevention of future OVEs.

For patients with MI, ASA followed by clopidogrel appears to be a cost-effective approach to the prevention of future OVEs.

For patients with established PAD or MVD, clopidogrel followed by ASA appears to be a cost-effective approach to the prevention of future OVEs.

8.1 Suggested research

It is suggested that any future trials in this area should distinguish between patients with single and multivascular disease, that definitions of MVD should be pre-specified (ideally using a common standard) and that trialists should ensure that trials are sufficiently powered over an extended follow-up period to allow detection of treatment differences between subgroups of patients. To facilitate comparison of primary and secondary outcomes across relevant trials, all outcomes need to be reported consistently and at key time points.

It would be most valuable to have well-audited data on a defined patient group from a long-term clinical registry of all UK patients treated with antiplatelet agents. Such a data source could provide a basis for research and audit to inform future assessments of antiplatelet agents in patients with single and multivascular disease over the long-term.

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119. Antithrombotic Trialists Collaboration. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. The Lancet. 2009; 373(9678):1849-60.
120. Berger JS, Krantz MJ, Kittelson JM, Hiatt WR. Aspirin for the prevention of cardiovascular events in patients with peripheral artery disease: A meta-analysis of randomized trials. JAMA. 2009; 301(18):1909-19.
121. Halkes PHA, Gray LJ, Bath PMW, Diener HC, Guiraud-Chaumeil B, Yatsu FM, et al. Dipyridamole plus aspirin versus aspirin alone in secondary prevention after TIA or stroke: A meta-analysis by risk. J Neurol Neurosurg Psychiatry. 2008; 79(11):1218-23.
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10 APPENDICES

Appendix 1: Literature search strategies

EMBASE 2003-2009 Week 36

# ▲	Searches
1	Clinical trial/
2	Randomized controlled trial/
3	Randomization/
4	Single blind procedure/
5	Double blind procedure/
6	Crossover procedure/
7	Placebo/
8	Randomi?ed controlled trial$.tw.
9	Rct.tw.
10	Random allocation.tw.
11	Randomly allocated.tw.
12	Allocated randomly.tw.
13	(allocated adj2 random).tw.
14	Single blind$.tw.
15	Double blind$.tw.
16	((treble or triple) adj blind$).tw.
17	Placebo$.tw.
18	Prospective study/
19	or/1-18
20	Case study/
21	Case report.tw.
22	Abstract report/ or letter/
23	or/20-22
24	19 not 23
25	Ticlopidine/
26	Clopidogrel/
27	clopidogrel.ti,ab.
28	plavix.ti,ab.
29	90055-48-4.rn.
30	(asasantin retard or persantin retard).ti,ab.
31	DIPYRIDAMOLE/
32	dipyridamole.ti,ab.
33	58-32-2.rn.
34	or/25-33
35	(myocard$ infarc$ or MI).ti.
36	NSTEMI.ti,ab.
37	non ST segment elevation myocardial infarction.ti,ab.
38	stroke.ti.
39	Cerebrovascular Accident/
40	(cerebrovascular accident$ or CVA).ti.
41	Transient Ischemic Attack/
42	(isch?emic stroke or transient isch?emic attack$).ti,ab.
43	Unstable Angina Pectoris/
44	unstable angina.ti,ab.

45	peripheral arterial disease.ti,ab.
46	(TIA or TIAS).ti.
47	Heart Infarction/
48	or/35-47
49	24 and 34 and 48
50	limit 49 to (human and english language and yr="2003 - 2009")

MEDLINE August Week 4 2009

#▲	Searches
1	randomized controlled trial.pt.
2	randomized controlled trials/
3	randomi?ed controlled trial$.ti,ab.
4	random allocation/
5	double-blind method/
6	single-blind method/
7	(clin$ adj2 trial$).ti,ab.
8	((singl$ or doubl$ or trebl$ or tripl$) adj2 (blind$ or mask$)).ti,ab.
9	placebos/
10	placebo$.ti,ab.
11	random.ti,ab.
12	comparative study/
13	exp evaluation studies/
14	follow-up studies/
15	prospective studies/
16	(control or controls or controlled).ti,ab.
17	clinical trials, phase iv/
18	phase iv.ti,ab.
19	phase four.ti,ab.
20	phase 4.ti,ab.
21	post market$ surveillance.ti,ab.
22	or/1-21
23	Case report.tw.
24	Letter/
25	Historical article/
26	or/23-25
27	22 not 26
28	Ticlopidine/
29	clopidogrel.ti,ab.
30	plavix.ti,ab.
31	90055-48-4.rn.
32	asasantin retard.ti,ab.
33	persantin retard.ti,ab.
34	dipyridamole.ti,ab.
35	dipyridamole/
36	58-32-2.rn.
37	or/28-36
38	exp MYOCARDIAL INFARCTION/
39	(myocard$ infarc$ or MI).ti.

40	NSTEMI.ti,ab.
41	non ST segment elevation myocardial infarction.ti,ab.
42	stroke.ti.
43	CEREBROVASCULAR ACCIDENT/
44	(cerebrovascular accident$ or CVA).ti.
45	ISCHEMIC ATTACK, TRANSIENT/
46	(isch?emic stroke or transient isch?emic attack$).ti,ab.
47	ANGINA, UNSTABLE/
48	unstable angina.ti,ab.
49	peripheral arterial disease.ti,ab.
50	(TIA or TIAS).ti.
51	or/38-50
52	27 and 37 and 51
53	limit 52 to (english language and humans and yr="2003 - 2009")

Web of Science® – now with Conference Proceedings
2003-2009

Databases searched=SCI-EXPANDED (Science Citation Index Expanded)**, CPCI-S (**Conference Proceedings Citation Index-Science)

((Clopidogrel or dipyridamole or plavix or ticlopidine or asasantin or persantin) and (Occlusive vascular event* or ischaemic attack or TIA or ischaemic stroke or myocardial infarction or MI or heart infarction or Peripheral artery disease or cerebrovascular accident* or unstable angina or ST segment elevation))

Results: Document Type=(ARTICLE (1,257) OR REVIEW (265) OR PROCEEDINGS PAPER (110) OR MEETING ABSTRACT (93)) AND Languages=(ENGLISH)

Total: 1,725

The Cochrane Library

2003- Issue 3, 2009

Databases searched=SCI-EXPANDED (Science Citation Index Expanded)**, CPCI-S (**Conference Proceedings Citation Index-Science)

((Clopidogrel or dipyridamole or plavix or ticlopidine or asasantin or persantin) and (Occlusive vascular event* or ischaemic attack or TIA or ischaemic stroke or myocardial infarction or MI or heart infarction or Peripheral artery disease or cerebrovascular accident* or unstable angina or ST segment elevation)) in title, abstract or key words

- Cochrane Database of Systematic Reviews (Cochrane Reviews): 6
- Database of Abstracts of Reviews of Effects (Other Reviews): 6
- Cochrane Central Register of Controlled Trials (Clinical Trials): 279
- Health Technology Assessment Database (Technology Assessments): 6
- NHS Economic Evaluation Database (Economic Evaluations): 20

Total number of references identified: 5869 including duplicate references)

Total number of references identified: 5109 (excluding duplicate references, removed electronically)

Appendix 2: Quality assessment

Quality assessment of included RCTs

Checklist item	CAPRIE[25]	ESPS-2[29]	ESPRIT[55]	PRoFESS[56]
Randomisation				
Was the randomisation method adequate?	Yes	Yes	Yes	Yes
Was the allocation of treatment adequately concealed?	Yes	Yes	Yes	Yes
Was the number of participants randomized stated?	Yes	Yes	Yes	Yes
Baseline comparability				
Were details of baseline comparability presented?*	Yes	Yes	Yes	Yes
Were the groups similar for prognostic factors?	Yes	Yes	Yes	Yes
Eligibility criteria and co-interventions				
Were the eligibility criteria for study entry specified?	Yes	Yes	Yes	Yes
Were any co-interventions identified?	Yes	Yes	Yes	Yes
Blinding				
Were outcome assessors blinded to treatment allocation?	Yes	Yes	No*	Yes
Were administrators blinded to the treatment allocation?	Yes	Yes	No	Yes
Were patients blinded to the treatment allocation?	Yes	Yes	No	Yes
Was the of the blinding procedure assessed?	NS	NS	NS	NS
Withdrawals				
Any unexpected imbalances in drop-outs between groups? Were they explained or adjusted for?	No/NA	No/NA	No/NA	No/NA
Were ≥80% patients included in the final analysis?	Yes	Yes	Yes	Yes
Were reasons for withdrawals stated?	Yes	Yes	Yes	Yes
Was an intention to treat analysis included? Was this appropriate? Were appropriate methods used to account for missing data?	Yes	Yes	Yes	Yes
Outcomes				
Evidence of more outcomes measured than reported?	No	No	No	No*

NA=not applicable; NS=not stated; * auditing of outcome events was blinded
**results for extra outcomes reported in supplement

Quality assessment of identified systematic reviews

Review	Inclusion/ exclusion criteria addressed review questions?	Evidence of a substantial effort to search for all relevant research literature?	Validity of included studies adequately assessed?	Sufficient detail of individual studies?	Primary studies summarised appropriately?
Jones 2004[3]	Good	Good	Good	Good	Good
Leonardi-Bee 2005[5]	Fair	Good	Fair	Good	Good
Verro 2008[9]	Fair	Good	Fair	Poor	Good
De Schryver 2007[13]	Good	Good	Good	Good	Good
ATTC 2009[119]	Good	Good	Good	Good	Good
Berger 2009[120]	Good	Good	Fair	Good	Good
Halkes 2008[121]	Fair	NA	NA	Good	Good
Sudlow 2009[122]	Good	Good	Good	Good	Good

Quality assessment of included cost-effectiveness studies

Drummond 10 points checklist[53]	Annemans 2003[68]	Beard 2004[69]	Berger 2008[70]	Chen 2009[71]	Karnon 2005[72]	Matchar 2005[73]	Schleinitz 2004[74]	Delea 2003[75]	Palmer 2005[76]	Stevenson 2008[77]	Van Hout 2003[78]
Well-defined question	✔	✔	✔ /x	✔	✔	✔	✔	x	✔ /x	✔ /x	✔ /x
Comprehensive description of competing alternatives	✔	✔	✔	✔	✔	✔ /x	✔	✔	✔	✔	✔
Effectiveness established	✔ /x	✔ /x	✔ /x	✔ /x	✔ /x	✔ /x	✔ /x	✔ /x	✔ /x	✔ /x	✔ /x
All important and relevant costs and consequences for each alternative identified	✔	✔	✔	✔	✔	✔ /x	✔	✔	x	x	x
Costs and consequences measured accurately	✔ /x	✔	✔	✔ /x	✔	✔	✔	✔	✔ /x	✔ /x	✔ /x
Costs and consequences valued credibly	✔	✔	✔ /x	✔	✔ /x	✔ /x	✔	✔	✔ /x	✔ /x	✔ /x
Costs and consequences adjusted for differential timing	✔	✔	✔	✔	✔	✔	✔	✔	✔ /x	✔ /x	✔ /x
Incremental analysis costs and consequences	✔	✔ /x	✔ /x	✔ /x	✔	✔	✔	✔	✔ /x	x	✔
Sensitivity analyses to allow for uncertainty in estimates of costs or consequences	✔	✔ /x	✔ /x	✔	✔	✔ /x	✔	✔ /x	✔ /x	✔ /x	✔ /x
Study results/discussion include all issues of concern to users	✔	✔	✔	✔	✔	✔ /x	✔	✔	✔	✔	✔

✔ =fully addressed; ✔ /x=partially addressed; x=not addressed.

Appendix 3: Description of systematic reviews

Eight relevant SRs were identified via the electronic searches: Jones[3] Leonardi Bee,[5] Verro,[9] De Schryver,[13] ATTC,[119] Berger,[120] Halkes,[121] Sudlow.[122] The majority of these were of good quality; all but two[9, 121] of the reviews, were of generally good quality (ie were rated as good on three or more criteria out of five). These generally supported current guidance but highlighted the variety of patients, the different combinations of drugs and outcomes that have been assessed. No additional trials were identified from the reference lists of the identified SRs for inclusion in the review.

Identifying and assessing the quality of existing reviews allowed the AG to cross check for the identification of additional studies as well as to gain an understanding of the issues related to the combining of data in this complex area. The identified reviews served to demonstrate the heterogeneity of patient populations and interventions as well as the different approaches to data analysis.

The SRs are listed in the table below; most of the included studies assessed immediate-release rather than modified-release dipyridamole. One of the identified SRs was the Jones[3] review that underpins the current NICE TA90 guidance.[23] Three further SRs were updates of those reported by Jones;[3] their conclusions remained unchanged.[13, 119, 122] These SRs, although meeting the inclusion criteria, included a variety of patient populations. Although included in the Jones review,[3] the patient population in De Schryver[13] appears to be different to those described in the scope (those with an arterial vascular disease) and is therefore not comparable.

Of the four newly identified SRs (ie those that are not updates from Jones[3]) three examined dipyridamole (both MRD and the immediate-release version). These reviews had similar patient populations (previous IS or TIA) but Leonardi Bee[5] compared dipyridamole, with or without ASA, to ASA alone; the other two SRs[9, 121] only compared dipyridamole+ASA to ASA alone, thus this is the only comparison that can be considered. The conclusions of all three SRs are generally consistent and favoured the use of dipyridamole+ASA over ASA alone. All three concluded that recurrent stroke was reduced by dipyridamole+ASA as was the composite of non-fatal stroke, non-fatal MI and vascular death.

Overall, the SRs examine both modified-release dipyridamole (MRD) and the immediate-release version of dipyridamole. De Schryver[13] included three trials that used MRD, Leonardi Bee[5] included one trial using MRD and six using the immediate-release version. Halkes[121] (an update of Leonardi Bee[5]) included two trials employed MRD, the remainder used the immediate-release version. Verro[9] included two trials that employed MRD, the other four

used the immediate-release formula. In the Jones review,[3] all trials and economic reviews that investigated dipyridamole used the modified version.

The SR by Berger[120] investigated the effect of ASA (alone or with dipyridamole) on cardiovascular event rates in patients with PAD. Dipyridamole is not currently licensed in this population. The included patient population was wide and included groups who were post-operative. Treatment with ASA alone or with dipyridamole resulted in a non-significant decrease in the primary endpoint of cardiovascular events but a statistically significant reduction in non-fatal stroke. This suggests that ASA is of benefit to patients with PAD (in this wider population) for the prevention of stroke, which is consistent with the current guidance.[23]

Review	Title	Patient population	Trials using MRD/ immediate-release dipyridamole
Jones 2004[3]	A rapid and systematic review of the clinical effectiveness and cost effectiveness of clopidogrel and modified-release dipyridamole in the secondary prevention of occlusive vascular events	MI, IS, PAD, TIA	1/1
De Schryver 2007[13]*	Dipyridamole for preventing stroke and other vascular events in patients with vascular disease (Review)	Coronary artery disease, MI, angina pectoris, retinopathy, nephropathy, PAD, IS, TIA, amaurosis fugax	3/29
ATTC 2009[119]*	Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials	MI, IS,TIA	NA
Sudlow 2009[122]*	Thienopyridine derivatives versus aspirin for preventing stroke and other serious vascular events in high vascular risk patients (Review)	High vascular risk	NA
Leonardi-Bee 2005[5]	Dipyridamole for preventing recurrent ischaemic stroke and other vascular events	IS, TIA	1/7
Verro 2008[9]	Aspirin plus dipyridamole versus aspirin for prevention of vascular events after stroke or TIA: a meta-analysis	IS,TIA	2/6
Halkes 2008[121]	Dipyridamole plus aspirin versus aspirin alone in secondary prevention after TIA or stroke: a meta analysis by risk	IS,TIA	2/5
Berger 2009[120]	Aspirin for the prevention of cardiovascular events in patients with peripheral artery disease: a meta-analysis of randomized trials	PAD (many following surgical procedures)	unclear

MI=myocardial infarction; IS=ischaemic stroke; PAD=peripheral arterial disease; TIA=transitory ischaemic attack; MRD=modified-release dipyridamole; NA=not applicable
*denotes update of previously identified SR

Appendix 4: Additional publications associated with each of the main trials

Table of publications associated with each of the four main trials

CAPRIE[25]
Ringleb PA, Bhatt DL, Hirsch AT, Topol EJ, Hacke W, Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events I. Benefit of clopidogrel over aspirin is amplified in patients with a history of ischemic events.. Stroke. 2004 Feb;35(2):528-32.
Bhatt DL, Marso SP, Hirsch AT, Ringleb PA, Hacke W, Topol EJ. Amplified benefit of clopidogrel versus aspirin in patients with diabetes mellitus. AmJC. 2002;90:625-8.
Cannon CP, Investigators C. Effectiveness of clopidogrel versus aspirin in preventing acute myocardial infarction with patients with symptomatic atherothrombosis (CAPRIE trial). AmJC. 2002;90:760-2.
Bhatt DL, Chew DP, Hirsch AT, Ringleb PA, Hacke W, Topol EJ. Superiority of clopidogrel versus aspirin in patients with prior cardiac surgery. Circulation. 2001;103:363-8.
Bhatt DL, Foody J, Hirsch AT, Ringleb P, Hacke W, Topol EJ. Complementary, additive benefit of clopidogrel and lipid-lowering therapy in patients with atherosclerosis. J Am Cardiol. 2000;35(Supplement A):326.
Bhatt DL, Hirsch AT, Ringleb P, Hacke W, Topol EJ. Reduction in the need for hospitalisation for recurrent ischemic events and bleeding with clopidogrel instead of aspirin. CAPRIE investigators. Am Heart J. 2000;140:67-73.
Hacke W, Hirsch AT, Topol EJ. The benefit of clopidogrel over aspirin is amplified in high-risk subgroups with a prior history of ischaemic events. Eur Heart J. 1999;20(abstract supplement).
Harker LA, Boissel JP, Pilgrim AJ, Gent M. Comparative safety and tolerability of clopidogrel and aspirin. Results from CAPRIE. Drug Saf. 1999;21:325-35.
Hacke W. On Behalf of The CAPRIE I. Consistency of the Benefit of Clopidogrel over Aspirin in Patients with Lacunar and Non-Lacunar Stroke. Cerebrovasc Dis. 1998;8(4):51.
Easton JD. Benefit of clopidogrel in patients with evidence of cerebrovascular disease. Neurology. 1998;50.
Morais J. Use of concomitant medications in the CAPRIE trial: clopidogrel is unlikely to be associated with clinically significant drug interactions. Eur Heart J.19(Abstract):182.
Coccheri S. Distribution of Symptomatic Atherothrombosis and Influence of Atherosclerotic. Eur Heart J. 1998;19:227.
Blecic S. Atherothrombotic events often indicate disseminated atherosclerosis: Data from CAPRIE. Cerebrovasc Dis. 1998;8:34.
Hankey G. The risk of vascular ischaemic events in patients with various clinical manifestations of atherothrombosis: data from CAPRIE. Cerebrovasc Dis. 1998;8:30.
Rupprecht HJ. Consistency of the benefit of clopidogrel across a range of vascular-related endpoints: results from CAPRIE. Eur Heart J. 1998;19(Supplement):484.
Gent M. Benefit of clopidogrel in patients with coronary disease. Circul Res. 1997;96:2608-.
ESPS-2[29]
Ariesen MJ, Algra A, Kappelle LJ. Antiplatelet drugs in the secondary prevention after stroke: Differential efficacy in large versus small vessel disease? A subgroup analysis from ESPS-2. Stroke. 2006 Jan;37(1):134-8.
Diener HC, Darius H, Bertrand-Hardy JM, Humphreys M. European Stroke Prevention S. Cardiac safety in the European Stroke Prevention Study 2 (ESPS2). Int J Clin Pract. 2001;55:162-3.
Sivenius J, Cunha L, Diener HC, Forbes C, Laakso M, Lowenthal A. Second European Stroke Prevention Study: antiplatelet therapy is effective regardless of age. ESPS2 Working Group. Acta Neurol Scand. 1999;99:54-60.
Sivenius J, Cunha L, Diener HC, Forbes C, Laakso M, Lowenthal A. Antiplatelet treatment does not reduce the severity of subsequent stroke. European Stroke Prevention Study 2 Working Group. Neurology. 1999;53:825-9.
ESPRIT[55]
Algra A. Medium intensity oral anticoagulants versus aspirin after cerebral ischaemia of arterial origin (ESPRIT): a randomised controlled trial. Lancet Neurology. 2007 Feb;6(2):115-24.
Halkes PHA. [Acetylsalicylic acid and dipyridamole offer better secondary protection than acetylsalicylic acid only following transient ischaemic attack or cerebral infarction of arterial origin; the 'European/Australasian stroke prevention in reversible ischaemia trial' (ESPRIT)]. Ned Tijdschr Geneeskd. 2006
PRoFESS
Diener HC. The PRoFESS trial: Future impact on secondary stroke prevention. Expert Review of Neurotherapeutics. 2007 Sep;7(9):1085-91.
Diener HC, Sacco R, Yusuf S. Rationale, design and baseline data of a randomized, double-blind, controlled trial comparing two antithrombotic regimens (a fixed-dose combination of extended-release dipyridamole plus ASA with clopidogrel) and telmisartan versus placebo in patients with strokes: The Prevention Regimen for Effectively Avoiding Second Strokes trial (PRoFESS). Cerebrovasc Dis. 2007 May;23(5-6):368-80.

Appendix 5: Excluded publications with rationale

Excluded publications

	Published paper	Reason for exclusion
1	Bezerra DC, Bogousslavsky J. Antiplatelets in stroke prevention: the MATCH trial. Some answers, many questions and countless perspectives. Cerebrovasc Dis. 2005;20 Suppl 2:109-18.	review
2	Anand S, Yusuf S, Montague P, Chin SL. The effects of oral anticoagulants in patients with peripheral arterial disease: Rationale, design, and baseline characteristics of the Warfarin and Antiplatelet Vascular Evaluation (WAVE) trial, including a meta-analysis of trials. American Heart Journal. 2006 Jan;151(1):1-9.	not relevant intervention
3	Anand S, Yusuf S, Xie C, Pogue J, Eikelboom J, Budaj A, et al. Oral anticoagulant and antiplatelet therapy and peripheral arterial disease. New England Journal of Medicine. 2007 19;357(3):217-27.	not relevant intervention
4	Bakhru MR, Bhatt DL. Interpreting the CHARISMA study. What is the role of dual antiplatelet therapy with clopidogrel and aspirin? Cleveland Clinic Journal of Medicine. 2008 Apr;75(4):289-95.	review
5	Bhatt DL, Flather MD, Hacke W, Berger PB, Black HR, Boden WE, et al. Patients With Prior Myocardial Infarction, Stroke, or Symptomatic Peripheral Arterial Disease in the CHARISMA Trial. Journal of the American College of Cardiology. 2007 15;49(19):1982-8.	not relevant intervention
6	Bhatt DL, Fox KA, Hacke W, Berger PB, Black HR, Boden WE, et al. A global view of atherothrombosis: Baseline characteristics in the clopidogrel for high atherothrombotic risk and ischemic stabilization, management, and avoidance (CHARISMA) trial. American Heart Journal. 2005 Sep;150(3).	not relevant intervention
7	Bhatt DL, Fox KA, Hacke W, Berger PB, Black HR, Boden WE, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. The New England Journal of Medicine. 2006	not relevant intervention
8	Bhatt DL, Topol EJ. Clopidogrel added to aspirin versus aspirin alone in secondary prevention and high-risk primary prevention: Rationale and design of the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial. American Heart Journal. 2004 Aug;148(2):263-8.	not relevant intervention
9	Biller J. Antiplatelet therapy in ischemic stroke: Variability in clinical trials and its impact on choosing the appropriate therapy. Journal of the Neurological Sciences. 2009 15;284(1-2):1-9.	not RCT or SR
10	Bjorklund L, Wallander MA, Johansson S, Lesen E. Aspirin in cardiology--benefits and risks. International Journal of Clinical Practice. 2009 Mar;63(3):468-77.	not RCT or SR
11	Bowry ADK, Brookhart MA, Choudhry NK. Meta-analysis of the efficacy and safety of clopidogrel plus aspirin as compared to antiplatelet monotherapy for the prevention of vascular events. American Journal of Cardiology. 2008 Apr;101(7):960-6.	not relevant patient group
12	Brown J, Lethaby A, Maxwell H, Wawrzyniak AJ, Prins MH. Antiplatelet agents for preventing thrombosis after peripheral arterial bypass surgery. Cochrane Database of Systematic Reviews. 2008;(4)	not patient population
13	Cacoub PP, Bhatt DL, Steg PG, Topol EJ, Creager MA. Patients with peripheral arterial disease in the CHARISMA trial. European Heart Journal. 2009 January;30(2):192-201	not relevant intervention
14	Calvet D, Touze E, Mas JL. Adding aspirin to clopidogrel in secondary prevention of ischemic stroke: no significant benefits - Results of the MATCH study. Presse Medicale. 2006 Apr;35(4):679-82.	not relevant intervention
15	Cassar K, Ford I, Greaves M, Bachoo P, Brittenden J. Randomized clinical trial of the antiplatelet effects of aspirin-clopidogrel combination versus aspirin alone after lower limb angioplasty. British Journal of Surgery. 2005 Feb;92(2):159-65.	not relevant intervention
16	Chairangsarit P, Sithinamsuwan P, Niyasom S, Udommongkol C, Nidhinandana S, Suwantamee J. Comparison between aspirin combined with dipyridamole versus aspirin alone within 48 hours after ischemic stroke event for prevention of recurrent stroke and improvement of neurological function: a preliminary study. Journal of the Medical Association of Thailand. 2005 Nov;88 Suppl 3:S148-54.	not relevant patient group
17	Chaturvedi S. Acetylsalicylic acid + extended-release dipyridamole combination therapy for secondary stroke prevention. Clinical Therapeutics. 2008 Jul;30(7):1196-205.	review
18	Culebras A, Borja J, Garcia-Rafanell J. Triflusal versus aspirin for the prevention of stroke. Progress in Neurotherapeutics and Neuropsychopharmacology. 2008 Mar;3(1):13-33.	not relevant intervention
19	de Borst GJ, Hilgevoord AA, de Vries JP, van der Mee M, Moll FL, van de Pavoordt HD, et al. Influence of antiplatelet therapy on cerebral micro-emboli after carotid endarterectomy using postoperative transcranial Doppler monitoring. European Journal of Vascular and Endovascular Surgery. 2007	not relevant patient group
20	Diener HC, Bogousslavsky J, Brass LM, Cimminiello C, Csiba L, Kaste M, et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. Lancet. 2004 Jul;364(9431):331-7.	not relevant intervention

21	Diener HC, Bogousslavsky J, Brass LM, Cimminiello C, Csiba L, Kaste M, et al. Management of atherothrombosis with clopidogrel in high-risk patients with recent transient ischaemic attack or ischaemic stroke (MATCH): Study design and baseline data. Cerebrovasc Dis. 2004;17(2-3):253-61.	not relevant intervention
22	Diener HC, editor. Management of atherothrombosis with clopidogrel in high-risk patients with recent transient ischaemic attack or ischaemic stroke (MATCH): Rationale and study design. 5th World Stroke Congress; 2004 Jun 23-26; Vancouver, CANADA.	not relevant intervention
23	Diener HC. Management of atherosclerosis with clopidogrel in high-risk patients with recent transient ischaemic attack or ischemic stroke (MATCH): study results. Stroke. 2004	not relevant intervention
24	Donnelly R. Antiplatelet therapy and prevention of ischaemic events: CAPRIE. British Journal of Diabetes and Vascular Disease. 2005 Jul;5(4):203-6.	not RCT or SR
25	Eikelboom JW, Hankey GJ, Thom J, Claxton A, Yi Q, Gilmore G, et al. Enhanced antiplatelet effect of clopidogrel in patients whose platelets are least inhibited by aspirin: a randomized crossover trial Journal of Thrombosis & Haemostasis. 2005 Dec;3(12):2649-55.	not relevant intervention
26	Einhaupl K. ESPRIT study design and outcomes-a critical appraisal. Current Medical Research & Opinion. 2007 Feb;23(2):271-3.	review
27	England T, Bath P. Safety and tolerability of clopidogrel when added to aspirin and dipyridamole in high risk patients with recent ischaemic stroke: a randomised controlled trial. 3rd UK Stroke Forum Conference 2008	not relevant intervention
28	England TJ, Bath PM. Triple antiplatelets for reducing dependency after ischaemic stroke (TARDIS). Safety and tolerability of clopidogrel when added to aspirin and dipyridamole in high risk patients with recent ischaemic stroke: A randomized controlled trial. International Stroke Conference 2009	not relevant intervention
29	Fox KA, Mehta SR, Peters R, Zhao F, Lakkis N, Gersh BJ, et al. Benefits and risks of the combination of clopidogrel and aspirin in patients undergoing surgical revascularization for non-ST-elevation acute coronary syndrome: the Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) Trial. Circulation 2004	not relevant patient group
30	Gorelick PB, Richardson D, Kelly M, Ruland S, Hung E, Harris Y, et al. Aspirin and Ticlopidine for Prevention of Recurrent Stroke in Black Patients: A Randomized Trial. Journal of the American Medical Association. 2003 11;289(22):2947-57.	not relevant intervention
31	Greisenegger S, Tentschert S, Weber M, Ferrari J, Lang W, Lalouschek W. Prior therapy with antiplatelet agents is not associated with outcome in patients with acute ischemic stroke/TIA. Journal of Neurology. 2006 May;253(5):648-52.	review
32	Halkes PHA, van Gijn J, Kappelle LJ, Koudstaal PJ, Algra A. Risk indicators for development of headache during dipyridamole treatment after cerebral ischaemia of arterial origin. Journal of Neurology Neurosurgery and Psychiatry. 2009 Apr;80(4):437-9.	review
33	Hart RG, Bhatt DL, Hacke W, Fox KA, Hankey GJ, Berger PB, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of stroke in patients with a history of atrial fibrillation: subgroup analysis of the CHARISMA randomized trial. Cerebrovasc Dis. 2008	not relevant intervention
34	Hills NK, Johnston SC. Trends in usage of alternative antiplatelet therapy after stroke and transient ischemic attack. Stroke. 2008 Apr;39(4):1228-32.	registry
35	Hradec J, Spinar J. [CHARISMA. The clopidogrel for high atherothrombotic risk and ischemic stabilization, management, and avoidance trial]. Cor et Vasa 2006	not relevant intervention
36	Huang YI, Cheng Y, Wu J, Li YS, Xu E, Hong Z, et al. Cilostazol as an alternative to aspirin after ischaemic stroke: a randomised, double-blind, pilot study. Lancet Neurology. 2008 Jun;7(6):494-9.	not relevant intervention
37	Ito E, Takahashi A, Kuzuhara S, Uchiyama S, Nakajima M, Riku S, et al. Ticlopidine alone versus ticlopidine plus aspirin for preventing recurrent stroke. Internal Medicine. 2003 01;42(9):793-9.	not relevant intervention
38	Karha J, Bhatt DL, Wolski K, Fox KA, Montalescot G, Topol EJ, editors. The use of COX-2 inhibitors and the risk of myocardial infarction in the clopidogrel for high atherothrombotic risk and ischemic stabilization, management, and avoidance (CHARISMA) trial. 79th Annual Scientific Session of the American-Heart-Association; 2006 Nov 12-15; Chicago, IL.	not RCT
39	Kennedy J, Hill MD, Ryckborst KJ, Eliasziw M, Demchuk AM, Buchan AM. Fast assessment of stroke and transient ischaemic attack to prevent early recurrence (FASTER): a randomised controlled pilot trial. The Lancet Neurology. 2007 Nov;6(11):961-9.	not relevant intervention
40	Mahmood A, Sintler M, Edwards AT, Smith SRG, Simms MH, Vohra RK. The efficacy of aspirin in patients undergoing infra-inguinal bypass and indentification of high risk patients. International Angiology. 2003 Sep;22(3):302-7.	not RCT
41	Mak KH, Bhatt DL, Shao M, Haffner SM, Hamm CW, Hankey GJ, et al. The influence of body mass index on mortality and bleeding among patients with or at high-risk of atherothrombotic disease. European Heart Journal. 2009 April;30(7):857-65.	not relevant intervention
42	Mak KH, Bhatt DL, Shao M, Hankey GJ, Easton JD, Fox KAA, et al. Ethnic variation in adverse cardiovascular outcomes and bleeding complications in the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) study. American Heart Journal. 2009 April;157(4):658-65.	not relevant intervention
43	Markus H. Antiplatelet therapy vs. anticoagulation in cervical artery dissection; Rationale and design of the Cervical Artery Dissection in Stroke Study (CADISS). International Journal of Stroke. 2007 Nov;2(4):292-6.	not a relevant population
44	Markus HS, Droste DW, Kaps M, Larrue V, Lees KR, Siebler M, et al. Dual antiplatelet therapy with clopidogrel and aspirin in symptomatic carotid stenosis evaluated using doppler embolic signal detection: the Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS) trial. Circulation. 2005 May 3;111(17):2233-40.	not relevant intervention
45	Matias-Guiu J, Ferro JM, Alvarez-Sabin J, Torres F, Jimenez MD, Lago A, et al. Comparison of triflusal and aspirin for prevention of vascular events in patients after cerebral infarction the TACIP study: A randomized, double-blind, multicenter trial. Stroke. 2003 Apr;34(4):840-7.	not relevant intervention

46	McKevitt FM, Randall MS, Cleveland TJ, Gaines PA, Tan KT, Venables GS. The benefits of combined anti-platelet treatment in carotid artery stenting. European Journal of Vascular and Endovascular Surgery. 2005 May;29(5):522-7.	not relevant intervention
47	Secondary stroke prevention set to benefit from PRoFESS trial: extended-release dipyridamole plus aspirin (Asasantin Retard) and clopidogrel share very similar benefit-risk ratio in vascular prevention. Cardiovascular Journal of Africa. 2008 May-Jun;19(3):165.	comment on PRoFESS
48	Serebruany VL, Malinin AI, Pokov AN, Hanley DF. Randomized single-blind 30-days trial of the antiplatelet profiles after extended-released dipyridamole and low dose aspirin versus clopidogrel with or without aspirin in diabetic patients after TIA. Cerebrovasc.Dis. 2008	not relevant intervention
49	Serebruany VL, Malinin AI, Ziai W, Pokov AN, Bhatt DL, Alberts MJ, et al. Effects of clopidogrel and aspirin in combination versus aspirin alone on platelet activation and major receptor expression in patients after recent ischemic stroke: for the Plavix Use for Treatment of Stroke (PLUTO-Stroke) trial. Stroke. 2005 Oct;36(10):2289-92.	not relevant intervention
50	Sprigg N, Gray LJ, England T, Willmot MR, Zhao L, Sare GM, et al. A randomised controlled trial of triple antiplatelet therapy (aspirin, clopidogrel and dipyridamole) in the secondary prevention of stroke: safety, tolerability and feasibility. PLoS ONE]. 2008;3(8):e2852.	not relevant intervention
51	Squizzato A, Keller T, Middeldorp S. Clopidogrel plus aspirin versus aspirin alone for preventing cardiovascular disease. Cochrane Database of Systematic Reviews. 2007	not relevant intervention
52	Thijs V, Lemmens R, Fieuws S. Network meta-analysis: simultaneous meta-analysis of common antiplatelet regimens after transient ischaemic attack or stroke. European Heart Journal. 2008 May;29(9):1086-92.	not relevant intervention
53	Uchiyama S, Fukuuchi Y, Yamaguchi T. The safety and efficacy of clopidogrel versus ticlopidine in Japanese stroke patients: Combined results of two Phase III,multicenter, randomized clinical trials. Journal of Neurology. 2009; 256(6):888-97.	not relevant intervention
54	Wang TH, Bhatt DL, Fox KAA, Steinhubl SR, Brennan DM, Hacke W, et al. An analysis of mortality rates with dual-antiplatelet therapy in the primary prevention population of the CHARISMA trial. European Heart Journal. 2007 Sep;28(18):2200-7.	not relevant intervention
55	Dieker HJ, French JK, Joziasse IC, Brouwer MA, Elliott J, West TM, et al. Antiplatelet therapy and progression of coronary artery disease: a placebo-controlled trial with angiographic and clinical follow-up after myocardial infarction. American Heart Journal. 2007 Jan;153(1).	not relevant intervention
56	Serebruany VL, Malinin AI, Pokov AN, Hanley DF. Antiplatelet profiles of the fixed-dose combination of extended-release dipyridamole and low-dose aspirin compared with clopidogrel with or without aspirin in patients with type 2 diabetes and a history of transient ischemic attack: A randomized, single-blind, 30-day trial. Clinical Therapeutics. 2008 Feb;30(2):249-59.	not relevant outcomes

Appendix 6: Identified ongoing trials

Table of ongoing trials

Trial name and identification no	Sponsor	Comparators	Aims of study	Study start date	Estimated primary completion date*	Estimated study completion date
Clopidogrel in High-risk Patients with Acute Non-disabling Cerebrovascular Events (CHANCE) NCT00979589	Ministry of Science and Technology of the People's Republic of China	CLOP+ASA (ASA will be replaced by placebo from day 21) Placebo+ASA	To assess the effects of a 3-month regimen of CLOP versus a 3-month regimen of aspirin alone on reducing the risk of any stroke when initiated within 24 hours of symptom onset in high-risk patients with TIA or minor stroke	July 2008	July 2011	December 2011
COMbination of Clopidogrel and Aspirin for Prevention of Early REcurrence in Acute Atherothrombotic Stroke (COMPRESS) NCT00814268	Sanofi-aventis	CLOP+ASA Placebo+ASA	To compare the efficacy of CLOP +ASA and ASA alone in preventing any recurrent ischaemic lesion	October 2008	December 2010	
Platelet-orientated Inhibition in New Transient Ischemic Attack (TIA) (POINT) Trial NCT00991029	University of California, San Francisco	CLOP+ASA Placebo+ASA	To evaluate CLOP as a treatment to reduce risk of stroke and MI after TIA in patients also prescribed ASA	October 2009	June 2016	
Secondary Prevention of Small Subcortical Strokes Trial (SPS3) NCT00059306	The University of Texas Health Science Centre at San Antonio	CLOP+ASA Placebo+ASA	To learn if CLOP+ASA is more effective than ASA alone for prevention of recurrent stroke and cognitive decline.	February 2003	June 2011	June 2011
Aspirin Non-Responsiveness and Clopidogrel Endpoint Trial (ASCET) NCT00222261	Ullevaal University Hospital	CLOP ASA	To investigate whether aspirin non-responders have a higher composite event rate than responders or whether CLOP treatment in patients non-responsive to aspirin will reduce their risk of future clinical events.	April 2003	July 2010	July 2010
JASAP: Japanese Aggrenox Stroke Prevention vs. Aspirin Programme NCT00311402	Boehringer-Ingelheim Pharmaceuticals	Aggrenox (MRD+ASA) ASA	To compare the preventative effect of recurrent stroke and safety of Aggrenox vs ASA	April 06	March 2009	

CLOP=clopidogrel; ASA= aspirin; TIA= transient ischaemic attack; MRD= modified-release dipyridamole;* Estimated date of final data collection for primary outcome measure

Appendix 7: Example of the MTC codes for the "First Ischaemic Stroke" and networks

```
model{
        for(i in 1:N){
#binomial likelihood
                        r[i] ~ dbin(p[i],n[i])

#Model for  first Ischemic Stroke based on three  trials
                         logit(p[i])<-mu[s[i]]+ d[t[i]] - d[b[i]]
                        }
# Fixed effect vague priors for the 3 trial baselines
for(j in 1:NS){
           mu[j]~dnorm(0,.0001)
                 }
d[1]<-0
#Give priors for log-odds ratios
           for (k in 2:NT){d[k] ~ dnorm(0,.001) }

#Absolute log odds on Treatment ASA based on 2 trials in which it was used
for (i in 1: N){
                 mu1[i] <- mu[s[i]]*equals(t[i],1)
                 }

#Calculate the mean treatment effects, T[k] on natural scale
for (k in 1:NT){
                  logit(T[k]) <- sum(mu1[])/ 2 + d[k]
                  }
#Rank the treatment effects (with 1=best) & record the best treatment
for(k in 1:NT){
                 rk[k]<- (NT+1) - rank(T[],k)
                 best[k]<-equals(rk[k],1)
                 best1[k]<-1-equals(rk[k],1)
                 }
# Calculate RR from OR by first generating probability of baseline comparator
#prior for the baseline comparator for each pair-wise comparison
p21.base~dbeta(0.5,0.5)
p31.base~dbeta(0.5,0.5)
p32.base~dbeta(0.5,0.5)

# likelihood
r21.base~dbin(p21.base, n21.base)
r31.base~dbin(p31.base, n31.base)
r32.base~dbin(p32.base, n32.base)

prob_baseline[1,2]<-p21.base
prob_baseline [1,3]<-p31.base
prob_baseline [2,3]<-p32.base
#All pair-wise log odds ratios and odds ratios
for (c in 1:(NT-1)){
           for (k in (c+1):NT ){
                     lor[c,k] <- d[k] - d[c]
                     log(or[c,k]) <- lor[c,k]
#All pair-wise relative risk
                     rr[c,k] <- or[c,k]/((1- prob_baseline [c,k])+(or[c,k]* prob_baseline [c,k]))
                     RRR[c,k] <-( rr[c, k]-1)
```

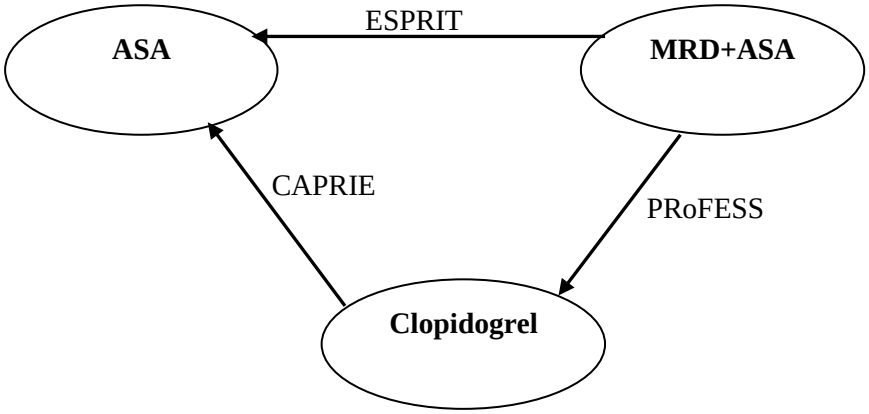

Figure 10-1 MTC network of RCTs 'first IS': ASA/clopidogrel/MRD+ASA

Solid black lines represent direct head-to-head comparisons and dotted lines represent indirect comparisons.

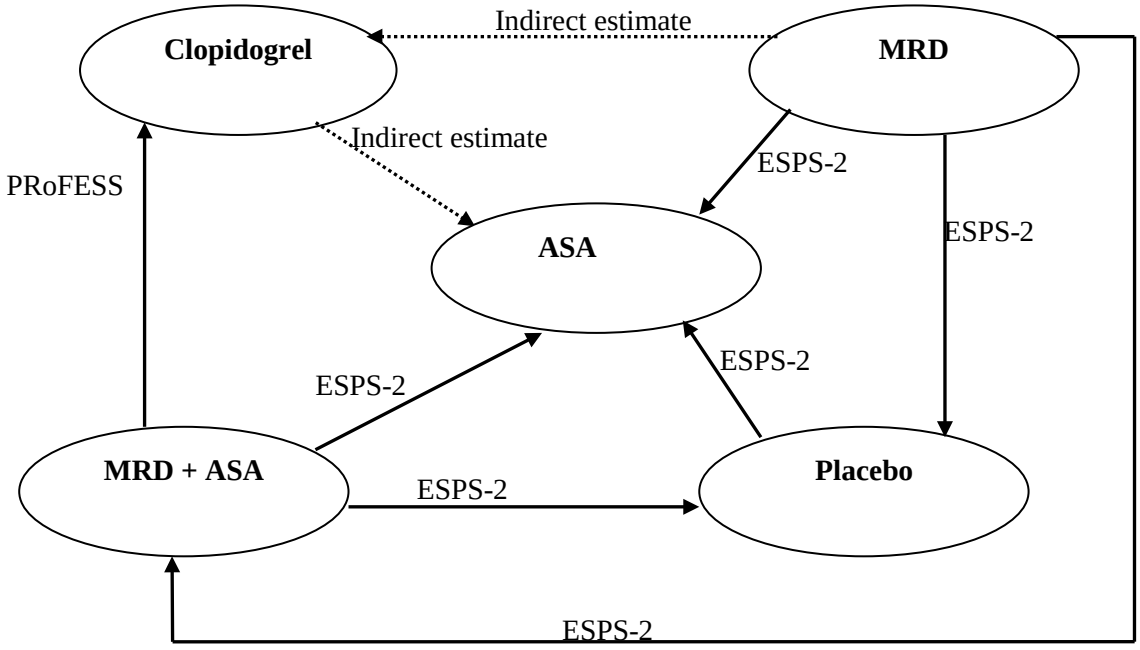

Figure 10-2 MTC network of RCTs 'recurrent stroke': ASA/clopidogrel/MRD+ASA

Solid black lines represent direct head-to-head comparisons and dotted lines represent indirect comparisons.

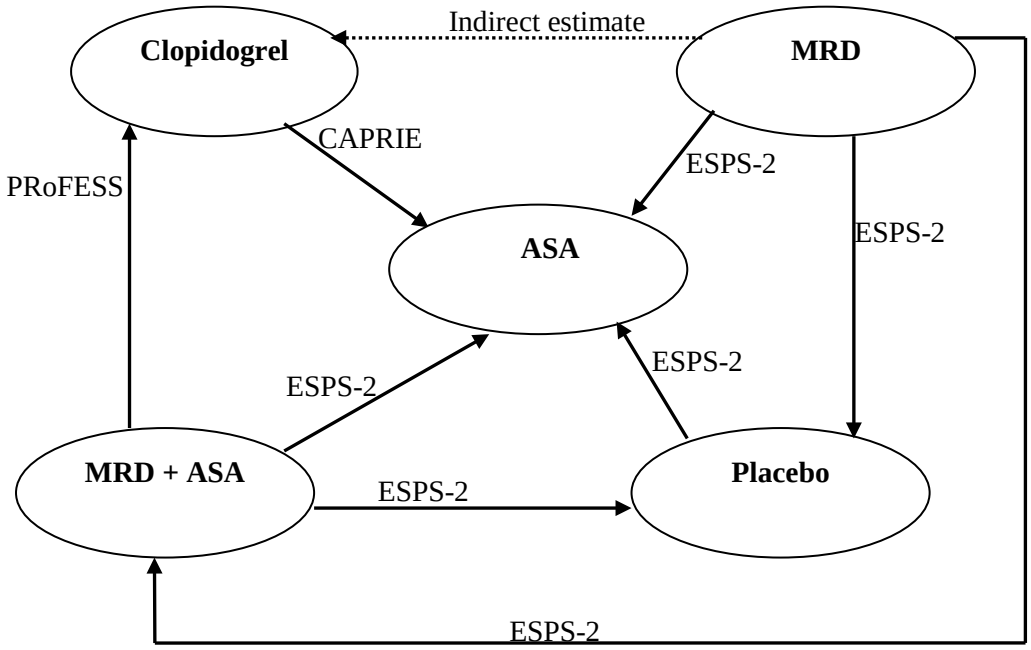

Figure 10-3 MTC network of RCTs 'MI': ASA/clopidogrel/ MRD+ASA

Solid black lines represent direct head-to-head comparisons and dotted lines represent indirect comparisons.

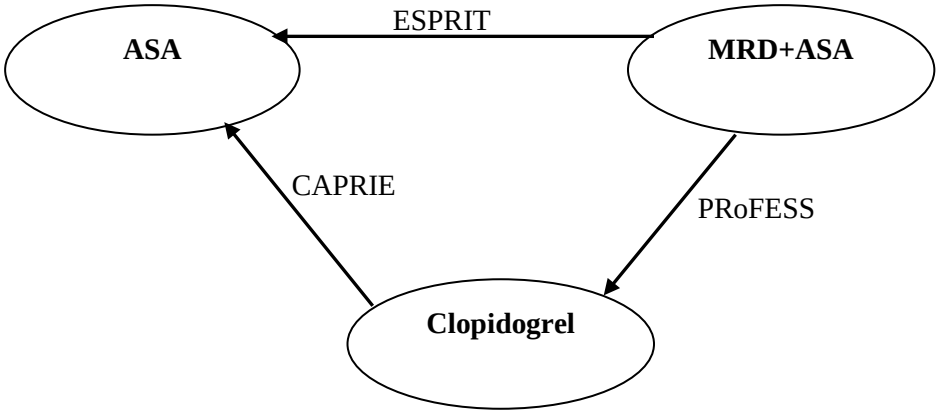

Figure 10-4 MTC network of RCTs 'death from vascular causes': ASA/clopidogrel/MRD+ASA

Solid black lines represent direct head-to-head comparisons and dotted lines represent indirect comparisons.

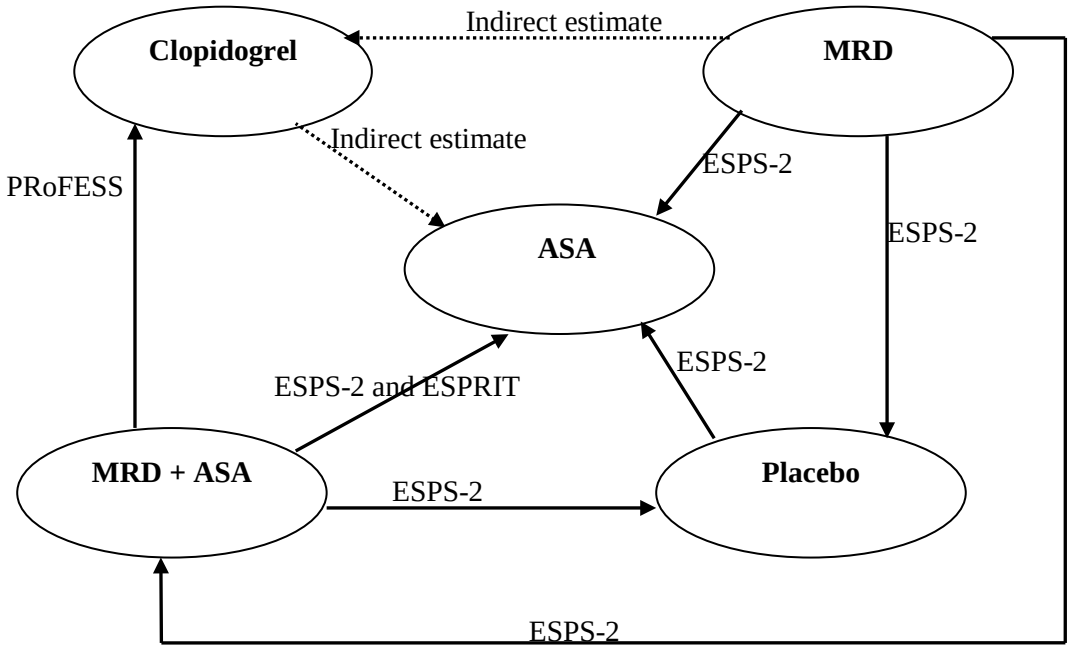

Figure 10-5 MTC network of RCTs 'all cause death': ASA/clopidogrel /MRD+ASA

Solid black lines represent direct head-to-head comparisons and dotted lines represent indirect comparisons.

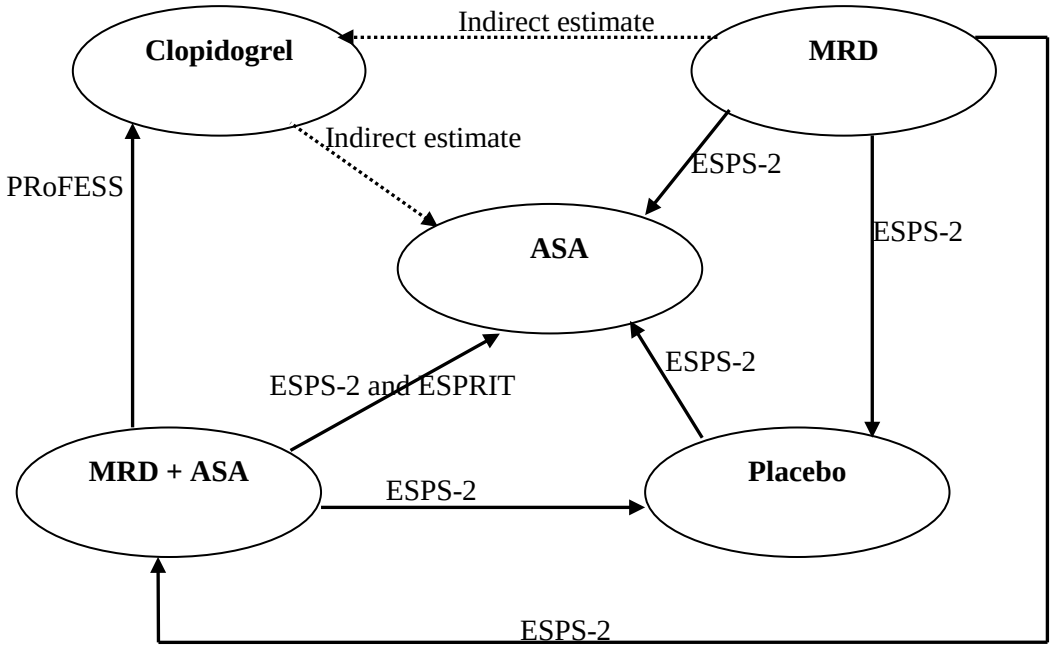

Figure 10-6 MTC network of RCTs 'any bleeding': ASA/clopidogrel/MRD+ASA

Solid black lines represent direct head-to-head comparisons and dotted lines represent indirect comparisons.

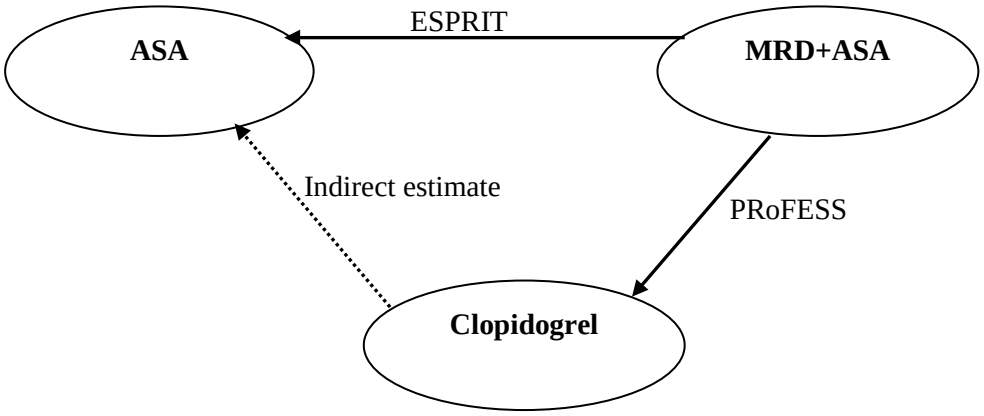

Figure 10-7 MTC network of RCTs 'death from major bleeding':ASA/clopidogrel/ MRD+ASA

Solid black lines represent direct head-to-head comparisons and dotted lines represent indirect comparisons

The codes used in the MTC analysis were adapted from the Multi-parameter Evidence Synthesis Research Group and are freely available for download from their website http://www.bris.ac.uk/cobm/research/mpes

Appendix 8: Sensitivity analysis table from review of cost-effectiveness literature

Sensitivity analysis

Study	Sensitivity analysis
Annemans 2003[68]	**One way SA: (ICER ranges)** Discounting rate: 0%-6% (€7,720-19,640), Increase and decrease a 50% costs of AE (ICER: €13,170-13,620), IS (ICER: €12,560-14,220) and life expectancy (ICER: €11,140-20,080). **PSA:** ICER: €14,320 (95% CI €6,990 to 26,470). 86% probability of be cost-effective at a threshold of €20,000
Beard 2004[69]	**Univariate SA:** (ICER ranges) Cost of acute stroke (ICER: £3,155-6959/QALY); Costs of OVE (£3,475-4,908 /QALY); Cost of TIA (£4,012-4,374 /QALY);Cost of long term care HD Stroke (cost saving £-8,757/QALY);Cost of long term care N/LD Stroke (£639-7,446/QALY);Cost of rehabilitation (£2,952-5,647/QALY); cost of ASA (cost saving £-4,801/QALY); RRR of ASA+MRD vs placebo (cost saving £-70,407 /QALY); Background events risks (£1,880-5,988/QALY); Initial disability level (£3,347-4,869/QALY); Disability risk after stroke (£3,053-5,888/QALY); utility weights stroke(£4,765-5,810/QALY). **PSA:** only with five parameters: 75% chance of being cost-effective at a £35,377 £/QALY threshold
Berger 2008[70]	**Univariate SA:** (ICER ranges)Treatment cost patients: scenario 1: €14,240-14,340/QALY, scenario 2: €18,840-18,740/QALY; AE event costs: scenario 1: €14,320-14,430/QALY, scenario 2: €18,710-18,870/QALY; concomitant medication costs: scenario 1: €14,370-14,380 /QALY, scenario 2: €18,780-18,800 /QALY; CLOP costs: scenario 1: €15,750 /QALY, scenario 2: €20,580/QALY; Discounting costs and effects: scenario 1: €8,350-18,610/QALY, scenario 2: €10,700-24,700/QALY. Discounting only costs 3%: scenario 1: €8,150/QALY, scenario 2: €10,440/QALY; discounting only effects at 3%: Discounting only costs at 3%: scenario 1: €14,740/QALY, scenario 2: €19,260/QALY
Chen 2009[71]	**Univariate SA:** (ICER ranges) Annual discount rate: $25,139-44,891/LYG; Lost life-years for cardiovascular deaths only: $51,033/LYG; lost life-years for non-fatal events: $31,771-42,453/LYG; CLOP costs average wholesale price: $16,176-56,520/LYG; post-acute care costs: $36,899-35,788/LYG: Including indirect costs from lost work productivity: $36,148/LYG. Variation of indirect cost from lost work productivity: $36,051-36,246/LYG. **PSA:** The probability of being cost effective at a threshold of <$50,000/LYG is 70.6% and 87.4% at <$100,000/LYG
Delea 2003[75]	ICER is sensitive to the assumed risk reduction for CLOP

Study	Sensitivity analysis
Karnon 2005[72]	**Univariate SA:** Health state costs (£21,333-21,819/QALY); Initial stroke costs (£24,683/QALY); trial based compliance (£16,528-24,683/QALY); utilities (£19,232-23,159/QALY); composite outcome RR (£12,835/QALY); RR for MI outcome (£20,026-23,383/QALY), RR for stroke outcome (£15,327-32,894/QALY), RR vascular death (dominated £-7,101 /QALY); RR for MI, stroke and vascular death (dominated -£5,602/QALY); inclusion of non- vascular death RR (£34,349/QALY); age at start 70 years (£16,222/QALY); age at start 80 years (£16,491/QALY); discount rate 6% for both costs and effects (£32,215/QALY); event rate x2 (£12,245/QALY); event rate x 0.5 (£41,486/QALY). Bivariate SA: (ICER ranges) Health state costs and utilities (£23,514/QALY). **PSA:** CLOP is cost effective at a threshold of £30,000/QALY in approximately 60% of randomly sampled analysis
Matchar 2005[73]	**Univariate SA:** (ICER) RR for ASA: PBO-ASA: $1,681-1,700/QALY; PBO-CLOP: $50,762-198,150/QALY; PBO-MRD+ASA: $1,769-1,769 /QALY. Costs based on Pharmacy Benefits Management Strategic Health Care Group. Drug & Pharmaceutical Prices: PBO-ASA: $1,562 /QALY; PBO-CLOP: dominated; PBO-MRD+ASA: $8,321 $/QALY. Efficacy limited to 24 months: PBO-ASA: $3,750/QALY; PBO-CLOP: dominated; PBO-MRD+ASA: $195,950/QALY. Accounting for impact of treatment on MI: PBO-ASA: $1,511/QALY; PBO-CLOP: $46,367/QALY; PBO-MRD+ASA: $1,667/QALY. **PSA:** ASA-MRD 65% probability of cost effectiveness at a threshold of $30,000/QALY
Schleinitz 2004[74]	**SA:** Efficacy of CLOP: PAD patients: $86,400-13,500 /QALY per QALY Post-stroke patients: $6300 / QALY- CLOP MI patients: more effective and cheaper in the base case to $42,000/QALY Daily cost of CLOP ($1.80 to $7.10): PAD patients: $14,900/QALY $ -41,800/QALY Stroke patients: dominance of CLOP- $85,500/QALY **PSA:** CLOP has a 50% probability of being cost effective at a threshold of $25,600/QALY for patients with peripheral vascular disease and $30,300/QALY for those with a recent stroke
Palmer 2005[76]	Paper states: "Sensitivity analyses showed that all results were robust under various assumptions"
Stevenson 2008[77]	**PSA:** The probability of the cost per QALY being below £20,000, a significant threshold for cost effectiveness in the UK, was 79%
Van Hout 2003[78]	Sensitivity analyses revealed that uncertainties surrounding the outcomes are mainly driven by the expected effectiveness, most notably when defining sub groups. The higher the risk for events, the better the cost effectiveness ratio. In comparison to no treatment (ASA intolerance or previous failure) CLOP is expected to combine gain in effectiveness (0.158 life years, 0.210 QALYs) with savings (€332 per patient)

SA=sensitivity analysis; ICER=incremental cost effectiveness ratio; AE=adverse events; PSA=probabilistic sensitivity analysis; QALY=quality adjusted life years; ASA=aspirin; MRD=modified-release dipyridamole; LYG=life years gained; RR=relative risk; MI=myocardial infarction; PBO=placebo; CLOP=clopidogrel; PAD=peripheral arterial disease;

Appendix 9: Additional data requested from manufacturers to populate the de novo model

Analyses requested by LRiG from the PRoFESS trial data

1. Survival Analyses

Kaplan-Meier analysis for each treatment arm, stratified by gender (male/female).
Cox proportional hazards analysis for treatment, using gender, age and Rankin score at time of prior event as covariates.

Run	Outcome estimated	Prior event(s)	Censored for
1	Time to ischaemic stroke	Randomisation	MI, non-ischaemic stroke, non-vascular death, death from any vascular cause other than ischaemic stroke
2	Time to non-ischaemic stroke	Randomisation	MI, ischaemic stroke, non-vascular death, death from any vascular cause other than non-ischaemic stroke
3	Time to MI	Randomisation	Any stroke, non-vascular death, death from any non-MI vascular cause
4	Time to other vascular death	Randomisation	MI, stroke, non-vascular death, death from MI or stroke
5	Time to non-vascular death	Randomisation	MI, stroke, vascular death
6	Time to vascular death	Randomisation	Non-vascular death
7	Time to death	Randomisation	Lost to follow-up or end of trial only
8	Time to other haemorrhagic event (excluding stroke)	Randomisation	MI, stroke, non-vascular death, death from MI or stroke
9-16	Repeat runs 1-8	Following non-fatal ischaemic stroke as first event	As for runs 1-8
17-24	Repeat runs 1-8	Following non-fatal non-ischaemic stroke as first event	As for runs 1-8
25-32	Repeat runs 1-8	Following non-fatal MI as first event	As for runs 1-8

MI= myocardial infarction

For each Kaplan-Meier analysis please provide full survival estimates table (e.g. “Product-Limit Survival Estimates” table from SAS, or the “Survival” table from SPSS) and the estimated means table (e.g. “Mean Estimate; table from SAS, or the “Means and Medians for Survival Time” table from SPSS). Cox analyses should show covariate coefficient estimates with confidence intervals.

2.Patient outcome events and exposure

For each of the following events for each treatment arm please provide a table showing trial numbers in the format shown:

Ischaemic strokes
Non-ischaemic strokes
MIs
Other haemorrhagic events (excluding strokes)
CHF events
Non-vascular deaths
Other vascular deaths (excluding strokes & MIs)
Vascular deaths

Time Period (months)	Exposure		All events			Fatal events		
	Patients at risk in period	Patient-days in period	1st trial event for patient	Other events	Total events	1st trial event for patient	Other events	Total events
0-6								
7-12								
13-18								
19-24								
25-36								
37-42								
43-48								

3. Event fatality

Please complete the following table for each subgroup by treatment arm, showing the proportion of each type of vascular event (occurring at any time) which was fatal, analysed by gender and age at the time of the event.

Gender	Age range	Ischaemic strokes			Intracerebral haemorrhages			MIs			Other Vascular Events		
		Events	Deaths	% fatal	Events	Deaths	% fatal	Events	Deaths	% fatal	Events	Deaths	% fatal
Females	<60												
	60-65												
	66-71												
	72+												
Males	<60												
	60-65												
	66-71												
	72+												

Appendix 10: Model risk parameter values and sources

For patients surviving an IS, four long-term treatment options are available to prevent future OVEs: low-dose ASA, clopidogrel, MRD and ASA+MRD. For the other three patient groups (MI only, PAD only and MVD) only ASA and clopidogrel are licensed for secondary prevention. In all cases it is also necessary to consider periods when no active long-term drug treatment is being taken to reduce the risk of OVE.

10.1 NICE Clinical Guidance CG48: post-MI clopidogrel

For patients suffering a new MI, recommendations were made in CG48[27] for the short-term use of clopidogrel+ASA to prevent early vascular events (primarily repeat MIs):

- for patients experiencing a NSTEMI, clopidogrel+ASA is recommended for 12 months

- for patients experiencing a STEMI, clopidogrel+ASA is recommended for 4 weeks (30 days)

The CURE[26] trial provides the evidence source for the first recommendation. This showed a significant protective effect in relation to repeat MIs, but not for strokes. The absolute risk reduction over 12 months was 1.47% (standard error 0.42%).

The recommendation for STEMI patients derives primarily from the COMMIT[28] trial where a modest reduction was seen in the rate of re-infarctions, but not in strokes. During the 30 day follow-up, an absolute risk reduction of 0.33% was reported (standard error 0.14%).

To accommodate the likely impact of these guidelines a weighted average effect has been estimated of 0.853% (standard error 0.207%), based on the balance of STEMI and NSTEMI patients in the GRACE[118] study (54.2% : 45.8%). This reduction is applied to the transient effect risk parameter values shown below for a second MI event after surviving a non-fatal MI, but not to any other MI risks which are much smaller, and where no transient effect was identified.

10.2 Risks of first OVE

10.2.1 Haemorrhagic stroke as first event

The annual risks of suffering an haemorrhagic stroke are generally very low, but vary significantly between patient types and between different treatment options. Reviewing all the data available, it appears that this risk is effectively constant over quite long periods of time. Evidence in some cases of a small additional early risk, is not confirmed from other sources, and may in part be a consequence of differing qualifying criteria among trials, so that some early acute events (in hospital or in the immediate post-discharge period) are counted within some trials but excluded in others. In estimating model parameters, such transient effects are ignored, and only the longer term annual event rate is employed.

For ASA and clopidogrel treatments, risks are estimated from the CAPRIE[25] trial; in the IS only population sufficient haemorrhagic stroke events were recorded to allow separate parameter values to be obtained, but for the other groups it was only possible to derive a single risk estimate for the population regardless of the treatment in use.

Haemorrhagic stroke risk for MRD+ASA treatment was estimated from the PRoFESS[56] trial (noting that the clopidogrel arm in PRoFESS[56] yielded a similar event rate to that in CAPRIE[25]). The risk appropriate for untreated patients was based on the ASA estimated relative risk for 'no treatment' vs ASA in an ATTC[65] analysis of secondary prevention published in 2002: 1.22 (1.03, 1.44). Finally, the annual risk of haemorrhagic stroke when using MRD was set at the same level as 'no treatment', based on the finding of very similar risks reported from the ESPS-2[29] trial.

Table 10-1Model parameter estimates for risk of haemorrhagic stroke as first event

Population	Detail	ASA	CLOP	ASA+MRD	MRD	No treatment
IS only	Annual risk	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Standard error	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Source	CAPRIE	CAPRIE	PRoFESS	CAPRIE / ATTC	
MI only	Annual risk	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Standard error	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Source	CAPRIE		[redacted]	[redacted]	CAPRIE / ATTC
PAD only	Annual risk	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Standard error	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Source	CAPRIE	CAPRIE	[redacted]	[redacted]	CAPRIE / ATTC
MVD	Annual risk	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Standard error	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Source	CAPRIE	CAPRIE	[redacted]	[redacted]	CAPRIE / ATTC

CLOP= clopidogrel; ASA= aspririn; MRD= modified release dipyridamole; IS= ischaemic stroke; MI= myocardial infarction; PAD= peripheral arterial disease; MVD= multivascular disease

10.2.2 Ischaemic stroke as first event

The risk of suffering a recurrent IS is relatively high for patients in the "IS only" and MVD populations. In addition to a long-term steady risk level, an important transient increased risk is also present within the trial data, which applies for slightly different periods for each population.

For the "IS only" population model parameter values have been estimated from CAPRIE[25] for ASA and clopidogrel, and from a comparison of PRoFESS[56] and CAPRIE[25] for ASA+MRD. The 'no treatment' risk was based on the ATTC[65] relative risk for ASA vs 'no treatment' applicable to ischaemic stroke. Finally, the annual risk of IS when using MRD was based on the MRD+ASA estimate adjusted by the relative risk reduction (24.7%) compared to MRD reported in the ESPS-2[29] trial. No consistent differences were observed in any of the trials relating to gender.

Table 1-2 Model parameter estimates for risk of IS as first event in the "IS only" population

Population	Detail	ASA	CLOP	ASA+MRD	MRD	No treatment
IS only	Long-term annual risk	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Standard error	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Transient risk	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Standard error	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Duration of transient risk (months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Source	CAPRIE	CAPRIE	PRoFESS / CAPRIE	ProFESS / CAPRIE / ESPS-2	CAPRIE / ATTC

CLOP= clopidogrel; ASA= aspririn; MRD= modified-release dipyridamole; IS= ischaemic stroke

In the "MI only" population, no consistent differences were found in the CAPRIE[25] data for the choice of treatment (ASA vs clopidogrel), but long-term risks were much higher for females than males. Therefore parameters were estimated for two models (males and females separately), combining patients in the two trial arms.

In the "PAD only" population, there was no evidence of differences by either gender or treatment so a single model was calibrated covering all CAPRIE[25] trial patients.

Table 1-3 Model parameter estimates for risk of IS as first event in the "MI only", "PAD only" and MVD populations

Population	Detail	ASA	CLOP	No treatment
MI only (females)	Long-term annual risk	[redacted]	[redacted]	[redacted]
	Standard error	[redacted]	[redacted]	[redacted]
	Transient risk	[redacted]	[redacted]	[redacted]
	Standard error	[redacted]	[redacted]	[redacted]
	Duration of transient risk (months)	[redacted]	[redacted]	[redacted]
	Source	CAPRIE	CAPRIE	CAPRIE/ ATTC
MI only (males)	Long-term annual risk	[redacted]	[redacted]	[redacted]
	Standard error	[redacted]	[redacted]	[redacted]
	Transient risk	[redacted]	[redacted]	[redacted]
	Standard error	[redacted]	[redacted]	[redacted]
	Duration of transient risk (months)	[redacted]	[redacted]	[redacted]
	Source	CAPRIE	CAPRIE	CAPRIE/ ATTC
PAD only	Long-term annual risk	[redacted]	[redacted]	[redacted]
	Standard error	[redacted]	[redacted]	[redacted]
	Transient risk	[redacted]	[redacted]	[redacted]
	Standard error	[redacted]	[redacted]	[redacted]
	Duration of transient risk (months)	[redacted]	[redacted]	[redacted]
	Source	CAPRIE	CAPRIE	CAPRIE/ ATTC
MVD (females)	Long-term annual risk	[redacted]	[redacted]	[redacted]
	Standard error	[redacted]	[redacted]	[redacted]
	Transient risk	[redacted]	[redacted]	[redacted]
	Standard error	[redacted]	[redacted]	[redacted]
	Duration of transient risk (months)	[redacted]	[redacted]	[redacted]
	Source	CAPRIE	CAPRIE	CAPRIE/ ATTC
MVD (males)	Long-term annual risk	[redacted]	[redacted]	[redacted]
	Standard error	[redacted]	[redacted]	[redacted]
	Transient risk	[redacted]	[redacted]	[redacted]
	Standard error	[redacted]	[redacted]	[redacted]
	Duration of transient risk (months)	[redacted]	[redacted]	[redacted]
	Source	CAPRIE	CAPRIE	CAPRIE/ ATTC

CLOP= clopidogrel; ASA= aspririn; MRD= modified-release dipyridamole; MI= myocardial infarction; PAD= peripheral arterial disease; MVD= multivascular disease

In the MVD population, there was equivocal evidence in CAPRIE[25] suggesting that females are at greater risk than males, and that ASA may be less effective than clopidogrel at preventing recurrent IS; however, the differences appeared to be quite small. In this case four separate models were calibrated to ensure that even small differences would be reflected in the economic results.

In all cases, risks for patients not receiving any prophylaxis were estimated by adjusting the ASA rates using the relative risk from the ATTC[65] meta-analysis.

10.2.3 Myocardial infarction as first event

The risk of suffering a MI is relatively high for patients in the "MI only" and MVD populations. In addition to a long-term steady risk level, an important transient increased risk is also present in some cases within the trial data, which applies for different periods for each population.

For the "IS only" population model parameter values have been estimated from CAPRIE[25] for ASA and clopidogrel where no difference was observed within the trial. A comparison of PRoFESS[56] and CAPRIE[25] allowed estimation of the long-term risk when receiving treatment with MRD+ASA. The 'no treatment' risk was based on the ATTC[65] relative risk for ASA vs 'no treatment' applicable to MI. Finally, the annual risk of MI when using MRD is assumed to be equal to that of 'no treatment' based on comparable event rates reported in the ESPS-2[29] trial. No consistent differences were observed in any of the trials relating to gender.

Table 1-4 Model parameter estimates for risk of MI as first event in the "IS only" population

Population	Detail	ASA	CLOP	ASA+MRD	MRD	No treatment
IS only	Long-term annual risk	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Standard error	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Transient risk	N/A	N/A	N/A	N/A	N/A
	Standard error	N/A	N/A	N/A	N/A	N/A
	Duration of transient risk (months)	N/A	N/A	N/A	N/A	N/A
	Source	CAPRIE	CAPRIE	PRoFESS / CAPRIE	CAPRIE / ESPS-2	CAPRIE / ATTC

CLOP= clopidogrel; ASA= aspririn; MRD= modified-release dipyridamole; IS= ischaemic stroke

In the "MI only" and "PAD only" populations, separate estimates of risk were obtained from the CAPRIE data for treatment with ASA and clopidogrel. No differences were apparent between males and females.

For the MVD population, there was some evidence in the CAPRIE[25] data supporting risk differences by both gender and treatment. Four separate models were calibrated to ensure that even small differences would be reflected in the economic results. Transient risks were only evident for ASA treatment.

In all cases, risks for patients not receiving any prophylaxis were estimated by adjusting the ASA rates using the relative risk from the ATTC[65] meta-analysis.

Table 1-5 Model parameter estimates for risk of MI as first event in the “MI only”, “PAD only” and MVD populations

Population	Detail	ASA	CLOP	No treatment
MI only	Long-term annual risk	[redacted]	[redacted]	[redacted]
	Standard error			
	Transient risk			
	Standard error			
	Duration of transient risk (months)			
	Source	CAPRIE	CAPRIE	CAPRIE / ATTC
PAD only	Long-term annual risk	[redacted]	[redacted]	[redacted]
	Standard error			
	Transient risk			
	Standard error			
	Duration of transient risk (months)			
	Source	CAPRIE	CAPRIE	CAPRIE / ATTC
MVD (females)	Long-term annual risk	[redacted]	[redacted]	[redacted]
	Standard error			
	Transient risk		N/A	
	Standard error		N/A	
	Duration of transient risk (months)		N/A	
	Source	CAPRIE	CAPRIE	CAPRIE / ATTC
MVD (males)	Long-term annual risk	[redacted]	[redacted]	[redacted]
	Standard error			
	Transient risk		N/A	
	Standard error		N/A	
	Duration of transient risk (months)		N/A	
	Source	CAPRIE	CAPRIE	CAPRIE/ ATTC

CLOP= clopidogrel; ASA= aspirin; MI= myocardial infarction; PAD= peripheral arterial disease; MVD= multivascular disease

10.2.4 Other vascular death as first event

The incidence of OVD as a first event in the "IS only" population was estimated directly jointly from the CAPRIE[25] trial data for ASA and clopidogrel treatments, where no meaningful differences were observed related to either choice of treatment or to gender. Analysis of the PRoFESS[56] trial results similarly shows no differences between clopidogrel and MRD+ASA. Occlusive vascular disease was not reported in other trials, but the ESPS-2[29] report allowed calculation of total deaths excluding fatal strokes and this was considered a reasonable proxy for OVD, allowing relative risk multipliers to be calculated for MRD and 'no treatment' compared to ASA+MRD.

Table 1-6 Model parameter estimates for risk of OVD as first event in the "IS only" population

Population	Detail	ASA	CLOP	ASA+MRD	MRD	No treatment
IS only	Long-term annual risk	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Standard error	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Transient risk	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Standard error	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Duration of transient risk (months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Source	CAPRIE	CAPRIE	PRoFESS / CAPRIE	CAPRIE / ESPS-2	CAPRIE / ESPS-2

CLOP= clopidogrel; ASA= aspirin; MRD= modified-release dipyridamole; IS= ischaemic stroke

In the "MI only" population, separate estimates of risk were obtained from the CAPRIE[25] data for treatment with ASA and clopidogrel, and for both genders.

In the "PAD only" population, no differences were observed by gender, so combined estimates were obtained for ASA and clopidogrel after combining results for males and females.

For the MVD population, there was clear evidence in the CAPRIE[25] data supporting risk differences by gender, but not by treatment. Therefore two models were calibrated for males and females.

In all cases, risks for patients not receiving any prophylaxis were estimated by adjusting the ASA rates using the relative risk from ESPS-2[29] trial as described above.

Table 1-7 Model parameter estimates for risk of OVD as first event in the "MI only", "PAD only" and MVD populations

Population	Detail	ASA	CLOP	No treatment
MI only (females)	Long-term annual risk	[redacted]	[redacted]	[redacted]
	Standard error	[redacted]	[redacted]	[redacted]
	Transient risk	[redacted]	[redacted]	[redacted]
	Standard error	[redacted]	[redacted]	[redacted]
	Duration of transient risk (months)	[redacted]	[redacted]	[redacted]
	Source	CAPRIE	CAPRIE	CAPRIE / ESPS-2
MI only (males)	Long-term annual risk	[redacted]	[redacted]	[redacted]
	Standard error	[redacted]	[redacted]	[redacted]
	Transient risk	[redacted]	[redacted]	[redacted]
	Standard error	[redacted]	[redacted]	[redacted]
	Duration of transient risk (months)	[redacted]	[redacted]	[redacted]
	Source	CAPRIE	CAPRIE	CAPRIE / ESPS-2
PAD only	Long-term annual risk	[redacted]	[redacted]	[redacted]
	Standard error	[redacted]	[redacted]	[redacted]
	Transient risk	[redacted]	[redacted]	[redacted]
	Standard error	[redacted]	[redacted]	[redacted]
	Duration of transient risk (months)	[redacted]	[redacted]	[redacted]
	Source	CAPRIE	CAPRIE	CAPRIE / ESPS-2
MVD (females)	Long-term annual risk	[redacted]	[redacted]	[redacted]
	Standard error	[redacted]	[redacted]	[redacted]
	Transient risk	[redacted]	[redacted]	[redacted]
	Standard error	[redacted]	[redacted]	[redacted]
	Duration of transient risk (months)	[redacted]	[redacted]	[redacted]
	Source	CAPRIE	CAPRIE	CAPRIE / ESPS-2
MVD (males)	Long-term annual risk	[redacted]	[redacted]	[redacted]
	Standard error	[redacted]	[redacted]	[redacted]
	Transient risk	[redacted]	[redacted]	[redacted]
	Standard error	[redacted]	[redacted]	[redacted]
	Duration of transient risk (months)	[redacted]	[redacted]	[redacted]
	Source	CAPRIE	CAPRIE	CAPRIE / ESPS-2

CLOP= clopidogrel; ASA= aspirin; MRD= modified-release dipyridamole; MI= myocardial infarction; PAD= peripheral arterial disease; MVD= multivascular disease

10.3 Risks of subsequent occlusive vascular events

For patients surviving a first OVE within the key trials (CAPRIE[25] and PRoFESS[56]), the number of patients suffering a second or third event are very small. In a few cases it is feasible to estimate parameter values relating to specific second events, but in many cases the data are insufficient, so it has been necessary to make assumptions based on the available evidence.

10.3.1 Following non-fatal IS as first event: Risk of second IS event

Nearly [redacted] of patients who survived an IS in the CAPRIE[25] trial went on to experience a second IS event. No significant differences in incidence rates were apparent relating to the choice of treatment. However, those belonging to the 'IS only' population experienced a lower level of risk than other patients. The same approach to extending these parameters to cover other treatments was employed as for IS first events.

Table 1-8 Model parameter estimates for risk of IS as second event following non-fatal IS as first event

Population	Detail	ASA, CLOP ASA+MRD*	MRD	No treatment
IS only	Long-term annual risk	[redacted]	[redacted]	[redacted]
	Standard error	[redacted]	[redacted]	[redacted]
	Transient risk	[redacted]	[redacted]	[redacted]
	Standard error	[redacted]	[redacted]	[redacted]
	Duration of transient risk (months)	[redacted]	[redacted]	[redacted]
	Source	PRoFESS / CAPRIE	ProFESS / CAPRIE / ESPS-2	CAPRIE / ATTC
MI only, PAD only & MVD	Long-term annual risk	[redacted]	N/A	[redacted]
	Standard error	[redacted]	N/A	[redacted]
	Transient risk	[redacted]	N/A	[redacted]
	Standard error	[redacted]	N/A	[redacted]
	Duration of transient risk (months)	[redacted]	N/A	[redacted]
	Source	CAPRIE	-	CAPRIE / ATTC

IS= ischaemic stroke; ASA= aspirin; CLOP= clopidogrel; MRD= modified-release dipyridamole; MI= myocardial infarction; MVD= multivascular disease; PAD= peripheral arterial disease; * not applicable to populations other than 'IS only'

10.3.2 Following non-fatal IS as first event: risk of MI event

Very few IS survivors suffered a subsequent MI in the CAPRIE[25] trial. A single overall linear regression hazard model was calibrated for all patient groups, extended additional treatments as before for first MI events.

Table 10-1-9 Model parameter estimates for risk of MI as second event following non-fatal IS as first event

Population	Detail	ASA, CLOP	ASA+MRD	MRD, no treatment
All patients	Long-term annual risk	[redacted]	[redacted]	[redacted]
	Standard error	[redacted]	[redacted]	[redacted]
	Transient risk	N/A	N/A	N/A
	Standard error	N/A	N/A	N/A
	Duration of transient risk (months)	N/A	N/A	N/A
	Source	CAPRIE	PRoFESS / CAPRIE	CAPRIE / ESPS-2 / ATTC

ASA= aspirin; CLOP= clopidogrel; MRD= modified-release dipyridamole

10.3.3 Following non-fatal IS as first event: risk of OVD event

Less than [redacted] of IS survivors in the CAPRIE[25] trial suffered a subsequent OVD event. A single projection model was calibrated for all patient groups, extended additional treatments as before for primary OVD events.

Table 1-10 Model parameter estimates for risk of OVD as second event following non-fatal IS as first event

Population	Detail	ASA, CLOP ASA+MRD	MRD	No treatment
All patients	Long-term annual risk	[redacted]	[redacted]	[redacted]
	Standard error			
	Transient risk			
	Standard error			
	Duration of transient risk (months)			
	Source	CAPRIE	PRoFESS / CAPRIE	CAPRIE / ESPS-2 / ATTC

ASA= aspirin; CLOP= clopidogrel; MRD= modified-release dipyridamole

10.3.4 Following non-fatal IS as first event: risk of HS event

Insufficient HS events occurred among IS survivors to allow any subdivision by patient subgroups or treatments.

Table 1-11 Model parameter estimates for risk of HS as second event following non-fatal IS as first event

Population	Detail	All treatments	No treatment
All patients	Long-term annual risk	[redacted]	[redacted]
	Standard error		
	Transient risk		
	Standard error		
	Duration of transient risk (months)		
	Source	CAPRIE	CAPRIE / ATTC

10.3.5 Following non-fatal MI as first event: risk of MI event

No differences in MI risk were detectable by treatment in the CAPRIE[25] trial data, but the risk among the MVD population was more than double the risk in the other groups.

Table 1-12 Model parameter estimates for risk of MI as second event following non-fatal MI as first event

Population	Detail	ASA, CLOP	ASA+MRD	MRD	No treatment
IS only MI only & PAD only	Long-term annual risk	[redacted]	[redacted]	[redacted]	[redacted]
	Standard error				
	Transient risk *				
	Standard error				
	Duration of transient risk (months)				
	Source	CAPRIE	PRoFESS / CAPRIE	CAPRIE / ESPS-2	CAPRIE / ATTC
MVD	Long-term annual risk	[redacted]	N/A	N/A	[redacted]
	Standard error		N/A	N/A	
	Transient risk *		N/A	N/A	
	Standard error		N/A	N/A	
	Duration of transient risk (months)		N/A	N/A	
	Source	CAPRIE	-	-	CAPRIE / ATTC

ASA= aspirin; CLOP= clopidogrel; MRD= modified-release dipyridamole; IS= ischaemic stroke; MI= myocardial infarction; PAD= peripheral arterial disease; MVD= multivascular disease; * these transient risks are further reduced by 0.853% for the short-term impact of CG48 guidance[27] as described above

10.3.6 Following non-fatal MI: risk of IS event

The risk of suffering an IS event following a non-fatal MI was found to be very low, and a single projective model was calibrated using all available CAPRIE[25] data.

Table 1-13 Model parameter estimates for risk of IS as second event following non-fatal MI as first event

Population	Detail	ASA, CLOP	ASA+MRD	MRD	No treatment
All patients	Long-term annual risk	[redacted]	[redacted]	[redacted]	[redacted]
	Standard error				
	Transient risk				
	Standard error				
	Duration of transient risk (months)				
	Source	CAPRIE	PRoFESS / CAPRIE	CAPRIE / ESPS-2	CAPRIE / ATTC

ASA= aspirin; CLOP= clopidogrel; MRD= modified-release dipyridamole

10.3.7 Following non-fatal MI: Risk of OVD event

Although it was not possible to detect any difference in risk by treatment type in the CAPRIE[25] data, it was clear that MVD patients suffered a three-fold risk of OVD following a non-fatal MI compared with other groups.

Table 1-14 Model parameter estimates for risk of OVD as second event following non-fatal MI as first event

Population	Detail	ASA, CLOP	ASA+MRD	MRD	No treatment
MI only, IS only, & PAD only	Long-term annual risk	[redacted]	[redacted]	[redacted]	[redacted]
	Standard error				
	Transient risk	N/A	N/A	N/A	N/A
	Standard error	N/A	N/A	N/A	N/A
	Duration of transient risk (months)	N/A	N/A	N/A	N/A
	Source	CAPRIE	PRoFESS / CAPRIE	CAPRIE / ESPS-2	CAPRIE / ATTC
MVD	Long-term annual risk	[redacted]	N/A	N/A	[redacted]
	Standard error		N/A	N/A	
	Transient risk	N/A	N/A	N/A	N/A
	Standard error	N/A	N/A	N/A	N/A
	Duration of transient risk (months)	N/A	N/A	N/A	N/A
	Source	CAPRIE	-	-	CAPRIE / ATTC

ASA= aspirin; CLOP= clopidogrel; MRD= modified-release dipyridamole; IS= ischaemic stroke; MI= myocardial infarction; PAD= peripheral arterial disease; MVD= multivascular disease

10.3.8 Following non-fatal MI: risk of HS event

The risk of HS following an initial MI event was found to be extremely low.

Table 1-15 Model parameter estimates for risk of HS as second event following non-fatal MI as first event

Population	Detail	All treatments	No treatment
All patients	Long-term annual risk	[redacted]	[redacted]
	95% confidence limits (LCL, UCL)	[redacted]	[redacted]
	Transient risk	N/A	N/A
	Standard error	N/A	N/A
	Duration of transient risk (months)	N/A	N/A
	Source	CAPRIE	CAPRIE / ATTC

LCL= lower confidence limit; UCL= upper confidence limit

10.3.9 Following non-fatal HS as first event

There were too few events of any type recorded in the CAPRIE[25] trial to patients surviving an initial HS. However, in order to provide parameters for this part of the model, a simple device was employed: the overall event rate was subdivided among the possible four types of event (IS, HS, MI and OVD) in proportion to their frequency among CAPRIE[25] first events, and the figure converted to a single average event rate for each event.

Table 1-16 Model parameter estimates for risk of second events following HS as first event

Population	Event	Detail	All treatments	No treatment
All patients	IS	Long-term annual risk	[redacted]	[redacted]
		Standard error	[redacted]	[redacted]
	HS	Long-term annual risk	[redacted]	[redacted]
		Standard error	[redacted]	[redacted]
	MI	Long-term annual risk	[redacted]	[redacted]
		Standard error	[redacted]	[redacted]
	OVD	Long-term annual risk	[redacted]	[redacted]
		Standard error	[redacted]	[redacted]
		Source	CAPRIE	CAPRIE / ATTC

IS= ischaemic stroke; HS= haemorrhagic stroke; MI= myocardial infarction; OVD= other vascular death

10.4 Risk modifiers

Cox's proportional hazard regressions were carried out on the CAPRIE[25] data to identify the influence of age and stroke-related disability (using the modified Rankin score) on the key first events in the trial. From these results event modifying factors were derived to allow the risk values described above to be adjusted to the characteristics of individual patients.

Table 1-17 Risk modifiers for age and stroke-related disability

Event	Age modifier	Stroke disability (modified Rankin score)	
	(per year)	Not disabled (0-2)	Disabled (3+)
Ischaemic stroke	[redacted]	[redacted]	[redacted]
Haemorrhagic stroke	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]
Other vascular death	[redacted]	[redacted]	[redacted]
Non-vascular death	[redacted]	[redacted]	[redacted]

Appendix 11: Event fatality rates estimated from CAPRIE trial data

Ischaemic stroke: There is only evidence to support differences in IS fatality risk arising from patient subgroup and age; gender and type of preventive treatment do not appear to be important predictors. An exponential odds model for risk increasing with age has been calibrated, with separate odds ratios applied for each patient group (greatest for MI only and PAD only patients and lowest for IS only patients). Fatality data from the PRoFESS[56] trial are not directly comparable, since the PRoFESS[56] population is a combination of IS only and MVD patients in unknown proportions. In addition, only the clopidogrel arms of the two trials could be included in any data synthesis. Nonetheless simple rate comparisons did not reveal any marked differences in fatality rates between the two sources.

Fatality odds = [redacted] * exp([redacted]*age)
* Population odds ratio
* Event sequence odds ratio

Odds ratios for patient subgroups are:

IS only	x [redacted]
MI only	x
PAD only	x
MVD	x

Odds ratios for event sequence (MIs or strokes):

1st	x [redacted]
2nd	x
3rd	x

Myocardial infarction: Myocardial infarction fatality is age and sex specific but is not influenced by the choice of treatment. Exponential odds models have been calibrated for exponential age relationships, separately for males and females. Important differences are apparent for population subgroups and for interactions between subgroups and sex, so separate age/group odds ratio modifiers are used. As noted above CAPRIE[25] and PRoFESS[56] data cannot be compared directly even with the IS population, but visual examination indicates that the PRoFESS[56] results are broadly consistent with those obtained from CAPRIE.[25]

For Females:

Fatality odds = [redacted]* exp([redacted]*age)
* Population odds ratio
* Event sequence odds ratio

Odds ratios for patient subgroups are:

IS only	x [redacted]
MI only	x
PAD only	x
MVD	x

Odds ratios for event sequence:

1st	x [redacted]
2nd	x
3rd	x

For Males:

Fatality odds = [redacted]* exp([redacted]*age)
* Population odds ratio
* Event sequence odds ratio

Odds ratios for patient subgroups are:

IS only	x [redacted]
MI only	x
PAD only	x
MVD	x

Odds ratios for event sequence (MIs or strokes):

1st	x [redacted]
2nd	x
3rd	x

Non-ischaemic stroke (HS): Small numbers of non-ischaemic strokes / intra cranial haemorrhages were reported in the two trials. When the fatality data from the CAPRIE[25] and PRoFESS[56] trials were combined, no significant differences attributable to age or patient population were detected so simple average rates have been estimated for age/treatment combinations:

Treatment	Males	Females
ASA	[redacted]%	[redacted]%
Clopidogrel	[redacted]%	[redacted]%
MRD + ASA	[redacted]%	[redacted]%
No treatment	30.0%*	55.0%*

* modeller's estimate in absence of relevant data